THE YEAR BOOK *of* DERMATOLOGY *and* SYPHILOLOGY

(1957 1958 YEAR BOOK *Series*)

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THE YEAR BOOK PUBLISHERS

INCORPORATED

200 EAST ILLINOIS STREET

CHICAGO 11

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INTRODUCTION

The International Congress of Dermatology in Stockholm was a major event of the year 1957 Dermatologists the world er owe a debt of gratitude to their Swedish col leagues for their great efforts and gracious hospitality which were nstrumental in making for an outstandingly successful Congress.

During the past year the new corticosteroids methylprednisolone and triamcinolon have been given extensive clinical trials However publications regarding their dermatologic effects have not appeared in time to permit their inclusion in this YEAR BOOK. Methylprednisolone (Medrol®) apparently has less effect on sodium and potassium metabolism than prednisolone and 4 mg is approximately as effective therapeutically as 5 mg prednisolone. Triamcinolone (Aristocort® and Kenacort®) a 9α-fluoro-16α-hydroxyprednisolone apparently lacks significant effect on sodium and potassium metabolism. A 3-4 mg dose of Triamcinolone is approximately as effective as 5 mg prednisolone. It is our impression as well as that of some of the other early investigators, that Triamcinolone in moderate doses is more beneficial n the treatment of certain dermatologic disorders (e g psoriasis) than the previously available compounds. Of course only additional experience will afford the ultimate answer regarding the advantages and disadvantages of these new drugs. It s noteworthy that after years of use of hydrocortison fo topical appl cation in patients of all age groups there is still no evidence of either allergic skin sensitization r sy temic side effects attributable to this compound.

New knowledge has been gained regarding the L.E. cell phenomenon and the serologic factors which produce it. Increasing interest is evident in the relationship between the chronic discoid form and the subacute and acute forms of lupus erythematosus. Recent studies have revealed findings in som pat ents with the chronic discoid form which suggest that the disease may not be restricted to the skin alone.

The use of ionizing radiations n the therapy of benign

dermatoses has become a matter of increasing discussion in medical as well as lay publications It is regrettable that in many of the articles on this subject in the lay press sensationalism rather than the endeavor to provide accurate information for the public appears to have been the principal motivation In such publications no differentiation is usually made between the effects of soft and hard forms of ionizing radiation From the dermatologic viewpoint it is important that simple technics have been worked out which reduce the gonad dose delivered during therapy of skin diseases to such an extent that they may ease or dispel the fears which have been created in many quarters. As has repeatedly been pointed out in these YEAR BOOKS the increasing use of the more superficial forms of ionizing radiation as employed by dermatologists is a move in the right direction.

During the past year fewer articles have appeared dealing with dermabrasion This subject has been well covered in recent years and its limitations and indications are better defined It is our impression also that the initial enthusiasm on the part of some dermatologists and of the public for this treatment has decreased

The role of the blood basophiles in urticaria and of the tissue mast cells not only in urticaria pigmentosa and systemic mastocytosis but also in allergic and nonallergic cutaneous reactions has attracted much interest Serotonin and histamine and their actions in various cutaneous responses are being intensively studied using histamine liberators antihistamines and serotonin inhibitors as investigative tools

Complete agreement exists among authors from various countries that a remarkable shift from T rubrum infections of the skin and nails to infections with other species of fungi is taking place

In this YEAR BOOK the editors have placed some of the abstracts of investigative studies with the clinical reports to which they pertain rather than restricting all investigative studies to one chapter as was done previously It is hoped that this innovation will increase the usefulness of the YEAR BOOK

THE EDITORS

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

A Review of Selected Aspects for the Practitioner

By RUDOLF L. BAER *and* VICTOR H. WITTEN

PART II

TEST PROCEDURES

In the leading article of the 1956-57 YEAR BOOK we discussed the clinical features of allergic eczematous contact dermatitis as well as its immunologic background, differential diagnosis and steps which must be taken in order to discover etiologic factors. Principal among the steps outlined in this search for etiologic agents were a carefully taken history and due consideration of the localization and course of the eruption.

If these steps clearly point to one or more agents as the cause of the presenting eruption, it is usually unnecessary to proceed with any tests. There are occasional exceptions to this, however, where medicolegal considerations demand that the physician present "black on white" proof of an existing allergic hypersensitivity to the suspected agent or agents.

When testing does become necessary to ascertain which, if any, among a group of suspected materials is causing the patient's eruption, a choice must be made between *clinical* testing ("use testing," "tests of avoidance and re-exposure") and *patch* testing. In most instances this decision favors the patch test method, an artificial procedure, rather than intentional re-exposure to a suspected agent under actual clinical conditions.

There are many reasons for this preference, but we should like to list the following as those of paramount importance: (1) Patch tests expose only a minute part of the skin's surface as against much larger areas usually exposed under actual clinical conditions. Obviously this may spare the pa-

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The names of authors who have done original work referred to in this article and the references to their work have been omitted from the text. A list of pertinent articles is given at the end of the article.

tient inconvenience discomfort and sometimes even incapacity (2) Patch tests permit exposure of suitable selected skin sites rather than the often highly inconvenient localizations *affected by actual clinical* exposure to suspected materials (3) Patch tests permit simultaneous testing of a series of suspected substances rather than laborious consecutive time-consuming clinical trials in which only one suspected substance is tested at a time. (4) Patch tests permit quantitation of *exposure regarding not only the size of* test areas but also the concentration of the test materials In this way the possibilities of severe or serious reactions are minimized.

These advantages are to some extent offset by the fact that the patch test an artificial *procedure cannot precisely* duplicate the actual conditions of clinical exposure There fore judging from the results of patch testing *alone* no reliable conclusions can be drawn regarding the culpability of any one allergenic substance. This is true whether the result of the test is positive or negative Despite this drawback however there can be little disagreement that patch tests are of the greatest value from the point of view of the clinician

In the leading article of the 1943 and 1944 YEAR BOOKS the details of patch testing for allergic eczematous contact sensitivity were set forth in much detail The principles and technics described at that time are today as valid as they were then *Nevertheless within the framework of this dis*cussion of allergic eczematous contact dermatitis it appears desirable to re-emphasize certain essential points which must be observed in attempts to find causal agents through testing We shall not go into the many well known technical details of patch testing except where newer developments make it desirable to do so

Laboratory and clinical test procedures cannot have much value unless they are carried out *lege artis* i e in the accepted completely standardized manner Therefore when applying and reading patch tests it is absolutely essential to adhere to certain established fundamentals The first and foremost rule—and peculiarly the one most frequently *broken—is that the con*centration of the test substance must be such that it does not elicit a reaction in nonsensitized skin The application of test substances in concentration

wh ch have the inherent capacity to irritate normal nonsensitized skin (i e., primary irritant concentrations) a priori makes it impossible to decide whether allergic sensitization does or does not exist. For example, even weak concentrations of toilet soaps, chrysarobin, anthralin and salicylic acid plus benzoic acid often produce some degree of skin reaction on nonsensitized skin. When the incidence of positive skin responses to a given concentration of such compounds is high among test subjects or even when only a small number of positive reactions is noted among presumably nonallergic control subjects then it is necessary to reconsider the possibility that these are primary irritant rather than allergic reactions If additional tests prove this assumption, it is essential to lower the concentration of the test material until it no longer acts as a primary irritant

The proper concentrations and vehicles for patch testing with a large number of substances have already been reliably established and may be found incorporated in various articles and books In testing with such allergens one should refer to these publications or to the re ised list presented at the end of this article

At times it becomes necessary to test with newly synthesized or othe agents for which proper patch test concentrations have not yet been established. Common sense is the first requirement n trying to arrive at the suitable concentration in such instances If the new substance is one wh ch is intended fo application to the skin or contact with the ki it is reasonable to assume that it can be tested as is without producing primary rritant reactions. There are exceptions however such as materials intended for use on the scalp palms, soles corns and calluses, all skin sites wh ch compared with most of the integument, are notorious for thei relatively high resistance to irritation If the ubstance is one wh ch i not designed for use on the skin, on should first consult the appropriate published lists for some similar or chemically related compound which is listed in ts proper concentration and vehicle for patch testing If this can be found the new substance should then be prepared for patch testing in equal or weaker concentration nd in the recommended veh cle. Should there be the suspicion that the newly prepared test substance w'll act as a primary rritant on normal nonsensitized skin it is best to

carry out control tests on presumably normal nonsensitized persons before applying it to the patient under investigation Should a particular substance or a closely similar one not be included in available patch test lists it would then be necessary to obtain all possible information about the new compound including its use toxicity irritating potential etc. After evaluating this information the new compound should be made up in the appropriate vehicle and in several test concentrations calculated to avoid primary irritant reactions on the skin of subjects presumed not to be allergic to the particular substance Any concentration which produces reactions in several or all of the "control subjects tested must be considered to possess primary irritant properties and is therefore unsuitable for testing the presumably allergic patient On the other hand any concentration to which only the patient responds with an eczematous reaction but to which control subjects do not react can be accepted as having elicited a specific allergic reaction

For example, a 1% ointment of anthralin (cignolin) almost always produces a primary irritant reaction on all the subjects to whom it is applied in contrast to a 1/30% ointment of anthralin which usually produces an eczematous reaction only in those with allergic sensitivity to this compound This is true also of many other materials such as soaps and shaving creams which are in common everyday use but which are applied in diluted form and are not usually placed under a semiocclusive dressing as they would be in a patch test While such materials ordinarily would not produce reactions under the conditions of normal usage they might well do so if applied in patch tests as is " that is in their original forms and concentrations

When testing with fumes or gases which are suspected of causing an allergic eczematous reaction special glass cups which resemble small thimbles with a rather broad smooth rim may be used Into such a cup a flat piece of felt or pledget of cotton which has been treated with the substance capable of producing the gas in question is introduced The open side of the cup is placed in contact with the skin It is held in place with adhesive tape for 48 hours when it is removed and the test read according to the standard technic All precautions concerning possible primary irritant reactions must be observed with gases as well as with solids and liquids

When selecting an area for patch tests it is best to choose nonhairy skin to permit optimal contact with the test substance Thus one also avoids unnecessary additional irritation often caused by removal of adhesive tape from a hairy region. If it is absolutely essential to use a hairy site it should be carefully shaved before testing

Whenever poss ble, a region ordinarily covered with clothing should be used. The extent of the covered area may vary tremendously depending on the patient s occupation social and economic status sex, geographic area in which he lives etc. In one patient the noncovered portions of the skin may be limited to the face and hands and in another they may include everything except the miniscule space covered by a Bikin bathing suit. Such precautions are taken in order to keep from iew any disfigurement which may be caused by a posit ve reaction which though usually mild and lasting for but a tew days or at most weeks, may be very severe in exceptional cases. In still rarer instances the test reaction may leave an unsightly mark for many years (depigmentation, hyperpigmentation scarring) The potential medicolegal aspects of such permanent cutaneous changes should always be borne in mind.

Of course when exquisite hypersensitivity to a test substance can be anticipated and t is decided nevertheless to proceed with a patch test, the patient should be told in ad ance of th possible immediate and late effects and consideration should be given to diluti g the test substance below the standard concentration. In any event, precautions should be taken in every case to remove any patch test as quickly as poss ble after the onset of burning, stinging or severe itching We have made it a rule to instruct patients to do this themselves mmediately if they cannot come to see us.

The back the most commonly used area of the body for routine patch testing with more than just a few substances. Pat hes should be placed beginning just below the houlders and xtend ng as low as the waist line the area immediately over the center of the sp ne should be voided since it is dif ficult to keep the adhesive tape patches in contact with the kin n this hollowed out area. If exceptional circumstances demand, as many as 50 or 60 patches may be applied to the back t ny one t me, but we usually prefer to make 30-40 the maximum umber When necessary arms, hips, thighs and

carry out control tests on presumably normal nonsensitized persons before applying it to the patient under investigation. Should a particular substance or a closely similar one not be included in available patch test lists, it would then be necessary to obtain all possible information about the new compound including its use toxicity irritating potential etc After evaluating this information the new compound should be made up in the appropriate vehicle and in several test concentrations calculated to avoid primary irritant reactions on the skin of subjects presumed not to be allergic to the particular substance Any concentration which produces reactions in several or all of the "control" subjects tested must be considered to possess primary irritant properties and is therefore unsuitable for testing the presumably allergic patient. On the other hand any concentration to which only the patient responds with an eczematous reaction but to which control subjects do not react can be accepted as having elicited a specific allergic reaction

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forearm, arm or thigh. Where this is not feasible the "open" test method may be used. This consists of dropping liquid test materials on an area of skin measuring about 1 cm. in diameter and allowing it to dry. When the test material is an ointment a small quantity is thoroughly rubbed into an area about 1 cm. in size and all excess is removed from the site by careful wiping.

More recently attempts have been made to increase the accuracy and effecti eness of patch tests by altering their physical design so as to achieve better contact of the allergen with the skin. Various materials have been used to allow for even distribution of pressure over the surface of the patch bearing the allergenic material. One that has proved most ffecti e has been a thin layer of sponge rubber. While this refinement of the patch test technic may well make for more accurat and ntense patch test reactions, there is much to be learned about the effects of this change in technic until then, t cannot be recommended for routine use in place of the orthodox method with which so much experience has been accumulated. In particular it appears possible that the stand rd dilutions of some substances may well exh b t primary irrita t properties when applied under a pressure patch.

Patch tests should be left in place for 48 hours and kept dry during this t me. At the time of removal of the patches it is essential that the exact location of each test sit be appropriately marked. At first this may appear to be superfluous because the common evanescent primary irritant ery thema which can be seen when the pat hes are removed and which s produced by the adhes ve tape frequently demar cates ea h ind vidual test site. However this erythema has u ually disappeared after 20-60 m nutes when the tests are to be read and consequently it is not always possible to locate the exact site of each test. Moreover it may also be difficult to d tinguish between mild reactions to the tests themselves nd remnants of adhesive tape erythema. Therefore w th the removal of each pat h the exact location of the test material, whi h is not necessarily dentical with the location of the center of the adhes ve pat h, should be carefully outlined with a skin ma king pencil, eyebrow pencil or other suitable dicator.

Twenty to 60 minutes should be permitted to elapse be tween removal of the adh siv patches and reading of the

forearms may also be used. When only a few tests are indicated the inner aspect of women's upper arms and nonhairy parts of men's arms may be utilized.

There are occasions when particular skin sites must be used for testing, notably when localized sensitivity is suspected. For example, a patch test with lipstick may produce a negative result if applied to a back area, whereas the same test may prove positive if applied to skin closer to the lips, such as the V of the neck. When sensitivity is strictly limited to the lips, lipstick must be applied directly to the lips themselves.

While adhesive patches for testing can be "home made" very inexpensively, various suitable patches of the classic variety, namely the type with a central piece of impermeable cellophane or other plastic material, are commercially available in the United States (e.g., Elastopatch, Duke Laboratories). In recent years we have mainly used small ready-made dressings of adhesive plastic with a central square of gauze instead of cellophane (e.g., Band Aid Plastic Patch, Johnson & Johnson). The latter has been found particularly useful as it adheres to the skin exceptionally well and usually without need for additional reinforcing adhesive. Tests done at the New York Skin and Cancer Unit by the paired comparison method with both types of patches (i.e., those with cellophane centers and those with gauze in the center) revealed no significant differences in the type or intensity of reactions obtained.

Before applying patches to the skin of patients with allergic eczematous contact dermatitis, it is advisable to inquire of them if there is any pre-existing allergic sensitivity to adhesive tape. If there is even a suspicion of such a sensitivity, it is wise to test the patient first with several brands and types of adhesive tape, including transparent plastic tapes, masking tapes and the French "Neodermotest." This may be done by applying about 1 cm. square pieces of the various tapes to selected skin sites (e.g., the back, arm or thigh) and leaving them in place for 24-48 hours. Ordinarily the skin will tolerate at least one of these tapes. In the unusual event that a skin reaction is caused by all the adhesive material, the test substances must then be applied under ordinary gauze dressings, held in place with gauze bandages on the

*See editorial comment, page 170, this Year Book.

In general one can expect the morphology and intensity of patch test reactions to resemble to some degree, the eruption being nvestigated. In addition to the nonspecific primary rritant patch test responses which may be confused with true allergic positive reactions one must exclude such other noneczematous reactions as the pustular lesions caused by some heavy metals (nickel, arsenic iron etc.) especially in patients with atopic dermatitis the transient erythema and edema due to adhesive tape used in testing colored stains especially those caused by dyes which may give the skin a reddish hue maceration miliaria-like acneform, furunculoid or isomorph reactions peculiar erythematous and vesiculobullous reactions sometimes caused by the pressure of solid materials under the patches These latter reactions have oc curred with large solid pieces such as acrylic dentures as well as with small particles like scrapings from such dentures It is nteresting to observe that these pressure reac tions are by far most likely to occur in women during or after the menopause

A positiv patch test reaction demonstrates an eczematous hypersensitivity of a particular skin site, at a particular time and to a particular substance in the manner and concentration appl ed A positi e reaction alone unsupported by adequate additional evidence, is not of great clinical value. It is highly significant and meaningful from the clinical view point only when a history of exposure to a particular subta ce or its close immunochemical elative can be correlated w th an exacerbation of the eruption and when improvement or clearing of the eruption can be correlated with avoidance f such exposure.

Likewise, a negative patch test response usually is an n dication of the absence of allergic eczematous hypersensitiv it but before such a definite conclusion is reached certain other possibilities which may account for a negative reaction must be excluded. Among these are the rather uncommon periodic fluctuations n the body s level of allergic hyper sens ti ity loss of sensitiv ty and local anatom c differences between kin reas and strictly localized sensitivity All of these may be causes for negati e patch test reactions at cer ta n t mes or on certa n areas of the body

But perhaps more important than all these or other possi-

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results. This waiting time is necessary to allow the adhesive reaction to subside. Whenever possible but particularly when there are doubtful reactions it is advisable to reread all the tests after an additional 24 hours In order to facilitate accurate localization of the test sites at this later reading it is necessary to mark each site carefully after the first reading This may be done with indelible marking pencils certain inks or preferably with very small adhesive strips placed on each side of each test area. Doubtful reactions noted at the first reading and which have disappeared by the time of the second reading usually may be considered negative doubtful reactions which have not faded but have become more intense should be considered positive on occasion delayed positive reactions may be noted at previously negative sites

The principles of proper reading and interpretation of patch test responses are exceedingly simple their practical utilization and proper application however can be learned only with experience. Difficulties are often encountered for example with reactions which on first reading (at the time the patches are removed) cannot be definitely interpreted and therefore are best called questionable. However when these reactions are reread the second time 24 hours later they can often be interpreted accurately

Ordinarily at least a definite erythematous reaction must be seen to justify a positive reading and incriminate a substance as the possible cause of a dermatitis. This is not the case however when a questionable or faint erythema is noted at the patch test sites of several substances in the same chemical group as for example crude coal tar liquor carbonis detergens Pragmatar* and Tarbonis creams (both of the latter contain tars) In such an event one must consider that the patient possesses an exceedingly mild allergic sensitivity to in this instance coal tar the ingredient common to all the preparations named

A reaction at the site of a patch test should be considered significant only if it is eczematous in character and has been elicited by the test substance which has been applied in standard concentration and according to conventional technics. Here we wish to emphasize that at times the slightest change in technic vehicle or concentration may create primary irritant conditions or false positive reactions due to other causes

TESTING WITH PREPARED SETS OF MATERIALS

Ideally every patient with allergic eczematous contact dermatitis should be tested with all those materials which are suspect in his case after a careful history has been taken. Such materials should then be freshly prepared in th proper vehicles in accordance with the appended list

Actually however especially in clinic practice it is not always feasible to adhere to this ideal and it becomes necessary to apply certain short cuts or routines for testing which in olve the use of already prepared sets of allergenic materials Routines such as these can never properly substitute for an individualized, careful work up of each case of allergic ec ematous contact dermatitis Nevertheless, it has been found that testing some patients with a well-chosen group of com *pounds may lead to discovery of* the allergenic agent causing th eczematous eruption under investigation

Selected groups of allergens may be made up in standard concentrations and in appropriate bases for "etiologic or therapeutic patch testing Etiologic" patch tests are de signed to find causal agents by using a set of allergens which in the particular locality nd at the particular time are among those which are most commonly incriminated as causal factors of allergic eczematous eruptions. "Therapeutic patch t sts a e those with selected items or sets of therapeutic agent includ ng selected veh cles as well as "active ingredients These are used to find out which medicaments may ha e caused a superimposed and perhaps spreading allergic contact dermatitis in a patient with an already existing eczematous eruption. "Therapeutic *patch tests* also are done to protect a patient from being treated with therapeutic agents to which he is already allergically sensitiv Usually uch tests are done only on selected patients who are suspected f previously having developed allergic sens tivity to rious topical medicaments. These tests are helpful only in ascertaining those medicaments to which the patient is already allergically sensitive and they obviously cannot foretell or prevent the development of sens tivity to add tional agents

The information gained from patch tests don with therapeutic substances commonly used in dermatologic therapy indeed most helpful in managing patients with chronic

ble explanations of negative patch test reactions to strongly suspected contact allergens is the fact that the patch test does not and cannot exactly duplicate the many and varied conditions of the actual clinical exposure. Thus the absence of a local patch test reaction only suggests but does not necessarily prove, that the substance tested was not the cause of the presenting dermatitis

Should patch tests be applied when there is an existing dermatitis especially an acute one? In considering this question it is well to realize that a markedly positive allergic patch test response may result in increased itching and exacerbation of existing sites of dermatitis sometimes in spreading and on very rare occasions in generalization of the eruption when there is a high degree of sensitivity to the test substance. Therefore if the presenting dermatitis is believed to be the result of a high degree of allergic sensitivity to a particular allergen it is advisable to wait at least until the acute phase of the dermatitis has subsided before applying a patch test with that suspected allergen When feasible we prefer *to wait still longer if possible until the eruption has subsided* This precaution reduces the chances of exacerbation of the existing dermatitis as well as other possible complications Moreover it tends to exclude the elicitation of false positive reactions known to occur during a hyperacute and particularly a widespread allergic eczematous dermatitis

Obviously there are times when it is not feasible to adhere to the principle of delaying patch testing in the presence of such a dermatitis For example in frequently recurring eruptions when it is impossible to avoid or remove all the suspected allergens it may be necessary to chance undesirable effects and proceed with the patch tests In persistent widespread eruptions such as severe perennial ragweed pyrethrum oleoresin contact dermatitis when there is no other hope of identifying the particular causal oleoresins except by testing patch tests often must be performed in the presence of an intense dermatitis

As has been mentioned previously systemic treatment with moderate doses of corticosteroids does not contraindicate patch testing since corticosteroids do little to alter allergic skin sensitivity particularly in a way that would interfere with the production of positive patch test reactions to allergens applied in standard concentrations.

TABLE 2—THERAPEUTIC AGENTS FOR PATCH TESTS

1 Arning's tincture, as is
2 Benzocaine 10% in alcohol
3 Coal tar (crude) 10% in petrolatum
4 Ammoniated mercury 10% in petrolatum
5 Liquor carbonis detergens, 10% in alcohol
6. Menthol, 1% in petrolatum
7 Oil of cade, 10% in petrolatum
8. Resorcin, 10% in water
9 Vioform® ointment (Ciba) as is
10 Anthralin ointment (Abbott) 1/30% (diluted with petrolatum)
11 Lanolin, as is
12 Pragmatar® (Smith, Kline & French) as is
13. Salicylic acid and ammoniated mercury as 2% in petrolatum
14 Boric acid, saturated solution
15 Burow's solution, 10% in water
16 Dermafton (Vacro) 10% in petrolatum
17 Sulfur ppt., 5% in petrolatum
18 Pyribenzamine® cream (Ciba) as is
19 Petrolatum (white) as is
20 Tarbonis cream (Reed and Carnrick) as is
21 Decalin ointment (Dome) as is
22 Chrysarobin, 1/20% in petrolatum
23 Quinadome cream (Dome) as is
24 Nupercainal® ointment (Ciba) as is
25 Quinolor compound ointment (Squibb) ½ strength (diluted with petrolatum)
26 Aureomycin ointment (Lederle) as is
27 Sterosan® ointment (Geigy) as is
28 Desenex ointment (Wallace and Tiernan) as is
29 Aluminum chloride, 10% in water
30 Procaine, 1% in petrolatum
31 Mycostatin® ointment (Squibb) as is
32 Myciguent® ointment (Upjohn) as is
33 Hydrocortisone acetate ointment, 2½% (Merck, Sharp and Dohme) as is
34 Cortef® ointment, 2½% (Upjohn), as is
35 Neosporin ointment (Burroughs Wellcome) as is
36 Plastibase® (Squibb) as is

containing medicaments, lipstick ingredients and nail polish ingredients, allergens encountered by workers in specific industries or occupations, groups of substances among which there may be cross-sensitizations, and many others.

While it is true that many substances made up in standard patch test concentrations will keep for years on the shelf, there are others which must be made up freshly at regular intervals to maintain their correct concentrations or chemical properties. In this category are preparations from which the active ingredient or vehicle may evaporate and leave a more or less concentrated solution of the test material, and unstable chemicals and materials containing ingredients

skin diseases for which many forms of treatment have been used and who state that one or more of these preparations have aggravated or caused flare-ups of their eruptions. Nondermatologists often fail to recognize the fact that a certain medicament while affording a patient temporary relief from itching for a variable period following its application at the same time may be aggravating or spreading the eruption simply because the patient possesses an allergic sensitivity to that very medication Thus positive reactions elicited in tests with selected therapeutic substances may help identify one or more of the preparations being used topically which are responsible for the persistence or spread of an existing dermatitis. At the same time by revealing which therapeutic substances do not produce reactions they may be of great help in selecting medicaments for further management.

Tables 1 and 2 list examples of groups of patch test substances currently being used at the New York Skin and Cancer Unit and in our private practices. We wish to reiterate that with the exception of the "therapeutic" tray we are not in favor of using prepared trays to seek out causal agents except in cases where practical circumstances preclude individual investigation of each case

In some situations it is helpful to have on hand trays of special patch test substances thus making readily available materials which otherwise would require much time to prepare. Examples of these are various ointment bases tars and tar

TABLE 1.—Routine Screening Tray

1. Paraphenylenediamine, 2% in petrolatum
2. Turpentine, 25% in olive oil
3. Mercury bichloride, 0.1% aqueous
4. Pyrethrum, as is
5. Nickel sulfate, 10% aqueous
6. Formalin, 5% aqueous
7. Lanolin, as is
8. Potassium dichromate, ½% aqueous
9. Ethylaminobenzoate, 5% in petrolatum
10. Linseed oil, as is
11. Ammonium fluoride 2% aqueous
12. Short ragweed oleoresin, in acetone (Graham)
13. Acrylic liquid monomer as is
14. Carbowax 1500, as is
15. Copper sulfate, 1% aqueous
16. Sodium arsenate, 10% aqueous
17. DDT 5% in acetone
18. Procaine, 1% in petrolatum
19. Poison ivy oleoresin, in acetone (Graham)

which underlie susceptibility to this form of sensitization.

As soon as allergic eczematous contact sensitization to a given allergen is established, complete avoidance of external contact or other routes of exposure to the allergen (or to im munochem cally closely related substances) is necessary to avoid recurrence of the dermatitis. It is obvious then that the role of the dermatologist is not merely to establish the cor rect diagnosis but to ascertain as well all the compounds wh ch may produce the dermatitis and then further to advise the patient concerning possible sources of exposure to the culpable allergenic substances and immunochemically closely related compounds

In mdustrial practice the dermatologist often finds prophylactic measures for avoidance of causal agents necessary These nclud wearing protective clothing such as gloves for the hands and masks for the face us ng "barrier creams for hands, wri t and fo earms introduction of such indus trial engineering measures as properly constructed exhaust ystem at the work bench, adequate ventilation enclosing of certa n hemical processes and, of course, adequate facil itres fo wa hing and showering changing cloth s, etc

I nonindustrial practice the dermatologist also is con fronted w th the problem of protect ve measures such as the use f ointments nd lotion d rectly on the skin. In recent year ter t has been focused on s licone-containing prod uct I ou experience silicone preparat ons, like other widely advertised protect e ompounds, ha e a limited and unpredictable usefulness in non ndustrial allergic eczematou con tact dermatitis. S licone ointments have been helpful in a small n mber of cases f dermatitis of the hands (we refer specifically to true allergic eczematous contact dermatitis nd not hand eczema in general) and they have proved impractical and useless in almost all cases of allergic eczematous contact dermat tis nvolving other areas. After several years of experience with the many d fferent commercially vailable il cone ointments, we have found that satisfactory res lt ha e been obta ned only with products with a very h gh licone content. Ha d lotions which are being sold now a cosmetics and which contain very mall quantities of sili con are worthles for the prophylactic purposes here under d scu ion

One might rightfully a k if it is reasonabl even to assume

which may react one with the other An illustration of the latter is an ointment containing ammoniated mercury and salicylic acid in which the two ingredients interact to form chemical compounds capable of producing primary irritant effects The danger also arises of cross-contamination between different bottles on a tray heavily used by more than one person in a busy clinic practice. It is therefore advisable to refill routinely all trays with freshly prepared test substances at interval of 6 months or less.

SOME REMARKS ON PROPHYLAXIS AND SPECIFIC TREATMENT

Unfortunately there are no known measures which can be depended on to prevent allergic eczematous contact sensitization in man except total avoidance of exposure to the allergens. Even this is not necessarily effective in preventing sensitization to a particular allergen since sensitivity can be acquired through cross sensitization Cross sensitization and its almost limitless possibilities have been previously discussed (1956-57 YEAR BOOK pp. 16-23)

In animals a rather meager beginning has been made in preventing allergic sensitization (producing tolerance) to an allergenic substance under certain conditions For example it has been shown in guinea pigs that feeding or intravenous or intracardial injection of an allergen before attempted sensitization by external contact to that same allergen definitely reduces their susceptibility to sensitization through such external contact Furthermore unpublished experiments suggest that ingestion of an [illegible] egnant guinea pigs may have a [illegible] on the sensitizability of ther off[illegible]

The question naturally arises as to whether or not these sketchy experimental observations in laboratory animals apply also to human beings Recently it has been suggested (see this YEAR BOOK p 115) that persons who have been exposed to contact with potent allergenic materials from rhus plants and to mango fruit by ingestion early in life subsequently show reduced susceptibility to contact sensitization to poison ivy There is an urgent need for more extensive studies since it appears unlikely that significant advance will be made in the field of prevention of allergic contact sensitization unless more is known about the basic factor

in some cases complete desensitization seems to have been accomplished.

The literature is replete with confusing reports on the efficacy of hyposensitization procedures in allergic eczematous contact dermatitis due to poison ivy and other plant oleoresins. The reasons for this confusion are readily apparent different investigators have utilized different sources for the allergenic plant different extracts vehicles, dosage schedules, periods of treatment routes of administration, types of subjects and to top off all these different criteria for evaluation of their results. When one adds the variations in opportunity for exposure to the allergenic plant and the differences in allergenicity even of the same plant from one year to the next, one soon realizes that the many variables involved in such studies make it entirely impossible to draw valid conclusions regarding the success or failure of a particular hyposensitizing procedure.

It stands to reason that most of the time the patient's statements about the occurrence or nonoccurrence of dermatitis during the few weeks or months following specific treatment are among the least reliable means of evaluating results of prophylactic treatment. For after all, people with a known allergic sensitivity to a particular plant, cosmetic, medicament etc usually consciously or unconsciously exert some degree of caution to avoid exposure to that substance even after hyposensitization treatment. It is difficult to understand exactly what is meant by clinical protection when the investigator has not re-exposed the patient under standardized and closely supervised conditions.

In our opinion the only evidence that can be relied on to evaluate the effectiveness of hyposensitization treatment are the results of clinical re-exposure under standardized and closely supervised conditions or *quantitative* patch tests done with the allergen after hyposensitization treatment and compared with the results of the same tests done before treatment and preferably also at intervals during treatment. Patch tests with quantitative dilutions of the allergenic materials permit the investigator to ascertain minor as well as major shifts in sensitivity. Perhaps it will be possible in the future to develop and utilize other procedures (serologic, hematologic etc.) to evaluate the effects of hyposensitization treatment

that ointments or lotions may some day be developed to protect against diverse allergens encountered under a variety of circumstances purely on the basis of a physical barrier type" mechanism. When considering the unending variety of allergens and factors which come into play with respect to such protection the idea of achieving such a panacea must be deemed rather utopian Theoretically more hope can be held out for the future of protective topical applications designed for neutralization inactivation and decontamination or what one might generally call deallergenization of specific compounds or groups of compounds Although steps in this direction have already been taken thus far they have been unsuccessful or have proved impractical for actual use. Preparations based on this principle of "deallergenization" which have not proved effective or useful for one reason or another include oxidizing compounds intended to inactivate poison ivy oleoresin BAL (dithiopropanol) compounds intended to inactivate certain heavy metal allergens and chelating agents intended to inactivate certain metal allergens

SPECIFIC PROPHYLAXIS AND TREATMENT

Efforts to lessen the allergic sensitivity of the skin of susceptible individuals by what today one would call specific hyposensitization were made long before von Pirquet and Schick developed the concept of allergy Unfortunately even today it must be admitted that attempts at such hyposensitization in allergic contact dermatitis have been generally unsuccessful despite the use of many different approaches It is obvious that with many common allergens hyposensitization by external application on large areas or by injection ingestion or inhalation of the allergen (starting with administration of minute doses and then gradually increasing the doses) is not practical for a variety of reasons It would not be feasible for instance to have a patient ingest or give him injections of nail polish or turpentine or one of the many other common contact type allergens nor would it be within reason to have him bathe in dilutions of nail polish or turpentine. Nevertheless there is increasing evidence that with certain allergens and under appropriate conditions a clinically significant reduction in the level of sensitivity can be achieved through hyposensitization treatment and

and streptomycin contact dermatitis has also been reported. The treatment, given by one author consisted of daily subcutaneous injections of minute doses of benzylpenicillin (crystalline penicillin). These doses consisted of a fraction of a unit to several units daily and were then gradually increased to amounts usually no greater than 20-25 units. After one to several weeks of such management, the antibiotic could usually be handled with little or no dermatitis resulting. Desensitization in penicillin contact dermatitis proved by patch test was also accomplished by oral administration of crystalline penicillin G starting with 50 units and increasing the dose daily. Intramuscular streptomycin, beginning with 10 mg. doses successfully desensitized patients highly allergic to this antibiotic.

Considering only those studies in which the results are based on supervised clinical re-exposure or on quantitative patch tests with the allergen before and after treatment one can infer that (1) "hyposensitization" at least with certain allergenic agents may be possible in allergic eczematous contact dermatitis, although the proportion of cases in which worthwhile results are achieved is not yet clearly apparent due to the relatively few cases which have been studied adequately to date. (2) it appears possible in some cases to achieve significant hyposensitization or complete desensitization to certain allergens (penicillin, streptomycin) during a relatively short period of time (weeks or months) with sufficiently low quantities of allergen that will not cause objectionable local or systemic side effects. (3) for certain other allergens (e.g. poison ivy, ragweed oleoresin) if one attempts to achieve significant or complete hyposensitization during a relatively short time (weeks) it often appears necessary to administer such large quantities of the responsible allergen that prohibitively severe local and systemic side effects are to be expected. (4) hyposensitization or complete desensitization to certain allergens (e.g. poison ivy, ragweed oleoresin) can be achieved with doses of the same allergen which usually do not cause severe local and systemic side effects provided relatively small doses can be given over a period of sometimes many months but usually 2 years or more. (5) the level of sensitivity in most patients successfully hyposensitized by means of either the short or pro-

If for the present, one considers standardized clinical re exposure or quantitative patch tests as the only acceptable criteria for evaluation of the therapeutic results of hyposen sitizing treatments then most studies published in the past 25 years on specific treatment of poison ivy dermatitis defy proper evaluation. However some studies have been published and are acceptable on the basis of these criteria as evidence that lessening of sensitivity can be deliberately en gendered. Examples of these are cases of allergic eczematous contact dermatitis due to oleoresins of certain plant aller gens, such as severe chronic and recurrent dermatitis due to the oleoresin of ragweed A number of patients at the New York Skin and Cancer Unit appear to have been completely desensitized by oral administration of ragweed oleoresin in corn oil over a period of 3 years This was shown by the re versal of a previously strongly positive to a negative patch test reaction to that substance. Using the method of Shel mire, treatment was started with 1 drop of a 1 100 concen tration of ragweed oleoresin in corn oil administered by oral capsule. The dose and concentration of the ragweed ex tract was gradually (if possible daily) increased until 12 drops of a 1 25 concentration was being given to the pa tient After the first year of treatment there was only a very slight noticeable favorable clinical effect after the second year a definite reduction in the severity of the eruption was observed and after the third year complete clearing was observed There were no serious side effects reported during this treatment Minor reactions appeared in the form of pru ritus and dermatitis in the perianal area resulting from con tact during defecation with the oily solution containing the allergen

Successful hyposensitization in ragweed oleoresin derma titis by the subcutaneous route has also been reported. In jections were given weekly starting with 0 1 cc. of a 1 1000 dilution of 10% ragweed oil in olive oil Apparently here also continual treatment for years is necessary to maintain ade quate protection. Desensitization to sulfonamides has been accomplished by daily oral administration of the sulfonamide in gradually increasing doses. Exceptional precautions are advised when attempting this method of desensitization to avoid severe generalized reactions

More recently successful hyposensitization in penicillin

tion of the potency of the poison ivy extracts in general use and the absence of treatment schedules which are individually planned for the patient and which take into account the degree of allergic hypersensitivity body weight, age, etc

The second of the common harmful measures too frequently used in the management of allergic eczematous contact dermatitis is the application of topical medicaments which themselves possess a high eczematogenic sensitizing potential. Numerous case reports, plus our own clinical experience and that of many of our colleagues leave no question as to the iatrogenic conversion of cases of acute allergic contact dermatitis into chronic eruptions through injudicious topical therapy It is our opinion that topical treatment with local anesthetics and antihistamines no matter what claims have been made for their supposed lack of allergenicity should be studiously avoided in the management of allergic contact dermatitis. Furthermore even when such external medicaments as tars, antibiotics, quinolines, quinaldines, etc., are being used, the possibility of their having caused a superimposed allergic contact dermatitis must always be considered when during treatment there is a sudden exacerbation of the dermatitis or when the acute phase of the original eruption continues unabated for an excessive period despite elimination of all known sources of exposure to the esponsible allergen.

It should be pointed out, nevertheless, that suitable topical treatment is definitely indicated in every case of allergic eczematous contact dermatitis and that, in addition other measures (oral antihistamines, systemic corticosteroids etc.) should be used when deemed necessary Topical therapy reduces nflammation and rel eves itching and is therefore a boon n preventi g the scratching and rubbing that so often interferes with spontaneous healing

SYSTEMIC TREATMENT WITH CORTICOSTEROIDS AND ACTH

We do not ntend to discuss at this time the various topical and systemic nonspecific measures wh ch ca be utilized allergic eczematous contact dermatitis. A few remarks regarding systemic treatment with ACTH and corticosteroids re in order however since this form of therapy gener lly not only hastens the involution of existing les ons but

longed method is likely to rise again within a period of weeks to months unless treatment is continued at regular intervals

SOME ERRORS IN TREATMENT

Allergic eczematous contact dermatitis with very rare exceptions is a self limited disease which clears on removal of the causal agents This spontaneous clearing can be expected within a few days to several weeks in the acute and subacute cases but may take many months in patients with chronic dermatitis In the exceptional cases in which clearing does not take place after removal of the etiologic agent it must be assumed that the eruption is being maintained by exposure to immunochemically related allergens i.e on the basis of cross sensitization or by other nonallergenic or allergenic factors which have supervened and which prevent a cure

In view of the self healing character of these eruptions treatment of allergic eczematous contact dermatitis should be limited to measures designed to relieve discomfort and to encourage or support its natural tendency to subside Conversely it seems especially unwarranted in what is ordinarily a harmless dermatosis to institute any measures which might prove harmful or might delay the natural course of involution of the lesions

We shall mention only two such potentially harmful measures which are especially risky but which nevertheless still enjoy considerable popularity among medical practitioners The first of these is the administration of specific allergenic extracts during the acute or subacute phase of the eruption This holds especially true in the treatment of poison ivy dermatitis with injections of poison ivy extracts There is neither a theoretical immunologic basis which would suggest that such injections should be efficacious in the short term treatment of such acute or subacute eruptions nor adequate empiric evidence to indicate that this treatment can be expected to give beneficial results On the contrary there is much evidence to show that in some cases administration of the responsible allergen produces highly unfavorable effects, such as exacerbations of the itching and of the lesions and even spreading of the eruption Even when there are immunologic bases for such treatment its potential harmfulness should not be surprising in view of the lack of standardiza

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particular stage of development which th dermatitis would have reached had no corticosteroid therapy been used. In other word at that point the patient is no worse off than he would ha e been if he had not received cortico teroid treatment.

SUMMARY

In the leading articles to the 1956-57 and 1957 58 YEAR BOOKS we have reviewed some of the basic immunologic and practical aspects of allergic eczematous contact dermatitis. Much is known with respect to clinical diagnosis, finding of causal factors and management of the disease in its various phases. The major remaining unsolved facets are the prevention of this form of sensitization and practical methods for abolishing established sensitivity. Progress with respect to these important problems is likely to be slow until more knowledge has been gained about the basic mechanisms which mediate and influence susceptibility to allergic eczematous contact sensitization.

SUBSTANCES, CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

		%	VEHICLE
Acetanilid	pdr	as is	
Acetic acid		3	aq.
Acetone		as is	
Acetphenetidin	pdr	as is	
Acridine*	pdr	pure	
Acrylic liquid monomer		as is	
AD (prop.)		1	aq.
Adhesive tape		as is	
Ajax (prop.)		1	aq.
Alcohol, denatured (controls)		as is	
Alcohol U.S.P.		70-95	
Aldehyde amines		as is	

Based on tables in Rostenberg, A., J., and Sulzberger, M. B.: J. Invest. Dermat., 1939, and Sulzberger, M. B., and Baer, R. L.: Year Book of Dermatology and Syphilology (Chicago: The Year Book Publishers, Inc., 1943); Sulzberger, M. B., and Baer, R. L. (eds.): Office Immunology (Chicago: Year Book Publishers, Inc., 1947).

Prepared in collaboration with Dr. Norman B. Kanof.

We are grateful also to Dr. Edwin Selz, Paris, and Prof. Hans Storck, Zurich, for their aid in bringing this list up to date.

Key to Abbreviations and Symbols

acet	=	acetone	Ger	=	German
alc	=	alcohol 70 per cent	o.o.	=	olive oil
aq	=	aqueous	pdr	=	powder
chlor	=	chloroform	pet.	=	petrolatum
[illegible]	=	castor oil	prop	=	proprietary preparation
controls	=	perform control tests on normal individuals	[illegible]	=	unfiltered
dext	=	15 per cent dextrose solution	sol	=	solution

*This substance may photosensitize the patch test area [illegible] after the patch has been removed and on exposure to light, dermatitis may supervene.

†This substance has been known to cause [illegible] sensitization of the eczematous type even after [illegible] single application to normal skin.

(Continued)

also many times prevents the development of new lesions

Systemic corticosteroid therapy is not indicated in routine management of allergic eczematous contact dermatitis but in a few cases provided there are no medical or psychiatric contraindications its use appears entirely justified We have found that it is impossible to set up hard and fast rules regarding the indications for prescribing these hormones. When making the decision whether to use such treatment or not we consider the severity and extent of the eruption the patient s age occupation economic and social responsibilities and many other factors which are difficult to define.

To control the more severe symptoms of itching and hold in check further rapid development of the eczematous eruption an average beginning dose of 150 mg cortisone or its equivalent of hydrocortisone, the delta derivatives or newer compounds (methylprednisolone or triamcinolone) is often sufficient, but in certain cases larger doses may be necessary and are justified As the dermatitis improves the dose of corticosteroids may be gradually reduced until it is finally discontinued. For example for a moderately severe case of poison ivy dermatitis a daily dose of 150 mg cortisone will usually have to be continued for 3-4 days Then it may be reduced to 125 mg and thereafter by 25 mg every second or third day Should an exacerbation follow one of these reductions in dose, the amount of the drug should be stepped up to its last effective level or even slightly higher and maintained at that level for several days before being reduced again In exceptional cases it may sometimes become necessary to maintain oral administration of one of the corticosteroids for many months The fact that corticosteroids within the dosage range discussed do not as a rule affect the patch test response to allergens has already been discussed

As previously pointed out topical medications should be used concomitantly with systemic corticosteroid treatment of allergic contact dermatitis Not only will it contribute to the patient s well being but it will often make it possible to reduce the amount of oral corticosteroids necessary to effect comfort and relief

Exacerbation or recurrence of the eruption may follow unduly rapid reduction in dosage or sudden discontinuation of corticosteroid or ACTH therapy The degree and intensity of the recurrence or exacerbation usually correspond to that

Arnica, tincture of	20-25	alc.
Arning tincture, modified (anthrarobin, tumenol ammonium, glycerin, spirits ether)	as is	
Aromatic oils	1	alc.
Arrid (prop.)	as is	
Arsenious trioxide pdr	pure	
Asphalt (no adhesive covering)	as is	
Aspirin	as is	
Atabrine	as is	
Atropine sulfate	1	aq.
Aureomycin ointment (prop.)	as is	
Auto lubricating oils	60	o.o.
Auto polishes (controls)	as is	
Azochloramid	0.2	triacetin
Bacitracin ointment	as is	
Bakelite (scrapings)	as is	
Baking powder	as is	
Baking soda	as is	
BAL (2-3 dithiopropanol)	as is	
BAL ointment (or in ethylene glycol)	as is	
Balata (rubber)	as is	
Balsam of Peru	10	pet.
Banana peel oil	pure	
Barbiturates	as is	
Barium hydrate	0.5	aq.
Barium sulfate	as is	
Barley oil	pure	
Bayberry oil of	25	o.
Bayberry oil of	25	pet
Beef fat oil	pur	
Beef salt	5	aq.
Beeswax	pure	
Beetle (prop.)	pure	
Benzaldehyde	10	aq.
Benzanthrone	pure	
Benzidine	pure	
Benzine	60	
Benzocaine	5	pet.
Benzoic acid	6	pet.
Benzoic anhydride	10	aq.
Benzol	60	o.
Benzophenone	1	aq.
Benzoyl amino-methoxychlor anthraquinone	2	o.
Benzyl alcohol	10	pet.
Benzyl benzoate	10	aq.
Benzyl chloride	5	aq.
Benzyl cinnamate	10	pet.
Bergamot, oil of*	10	pet.
Beryllium fluoride or other salt	1	aq. (buff to pH5)
Betahydroxy anthraquinone	1	alc.
Betanaphthol	10	o.o.
Beta-phenylacrylic acid	5	pet.
Bis (dimethylthiocarbamyl) disulfide	1	pet.
Bismarck brown-331	pure	
Bismogenol	as is	
Bismuth, colloidal solution	as is	

Continued)

Substances, Concentrations and Vehicles to Be Used in Patch Testing (Cont.)

Alizarin	pure	
Alizarin 778	1	alc.
Alizarin red 1034	pdr as is	
Alizarin sulfate	10	aq
Alkaloids—as salts	1	aq
Allspice	as is	
Almond oil	as is	
Alpha naphthylamine	pure	
Alum	10	aq
Aluminum acetate	10	aq.
Aluminum chloride	2	aq.
Aluminum scrapings	as is	
Alypin	1	aq.
Amber, oil of	*1*	alc.
Amido-azobenzol	2 10	o.o.
Amido-azotoluene hydrochloride	1	aq
Amidol	5	aq
Amidophenol (ortho- meta or para)	2 10	pet.
Amines	2	pet.
Amino-azotoluene	2	alc.
Amino-azotoluene	pdr as is	
Aminodracylic acid	1	alc.
Aminopyrine	as is	
Ammonia	1	aq
Ammonium bichromate	0.5	aq
Ammonium bichromate	0.5	pet.
Ammonium carbonate	15	aq
Ammonium chloride	3	aq.
Ammonium fluoride	0.5-2	aq
Ammonium nitrate	10	aq.
Ammonium persulfate	1.5	aq.
Ammonium sulfate	10	aq.
Amyl acetate	pure	
Analgesics	as is	
Anesthesin	5	pet.
Aniline	10-25	o.o.
Aniline black 870	pdr pure	
Aniline brilliant green	pdr pure	
Aniline dyes	*2*	o.o.
Aniline dyes	2	pet.
Aniline dyes	pdr pure	
Anise seed oil	25	c.o.
Anthracene	pure	
Anthralin (*1-8 dihydroxyanthranol*)	0.03	pet.
Anthraquinone	pdr pure	
Anthraquinone blue S R 1089	pure	
Anthrarobin	3	pet
Anticorrosion oils (controls)	as is	
Antihidrotic (prop.) (controls)	as is	
Antimony chloride	2	aq
Antimony oxide	pure	
Antipyrine	*as is*	
Aquaphor (prop.)	as is	
Aqua Velva (prop.)	*as is*	
Argyrol	10	aq
Arnica, tincture of	10-25	pet.

Dichloromate benzine	10	aq.
Diethylamino—ethanol	1	aq.
Diethylene glycol	10	aq.
Digalloyl trioleate	3 5	pet.
Dihydrostreptomycin	5	aq.
Diiodohydroxyquinoline	3	pet.
Dimethyl amine	pure	
Dimethyl aniline	10-25	o.o.
1-4 dichloronitrobenzene	1	acet.
1 4-2 dichloronitrobenzene	1	acet.
1-8 dihydroxy-anthranol	0 1	pet.
1-8 dihydroxy-anthraquinone	0.5	alc.
1 8 dihydroxy-anthraquinone	0 5	alc
1-4 dihydroxy-anthraquinone	0.5	alc.
1 2-4 dinitrochlorobenzene*	1	acet.
Dinitrocresol	5	chlor
2-4 dinitrophenol	10	aq
Dinitrotoluol	sat.	alc.
Di orthotolyl guanidine	pdr pure	
Di-orthotolyl thio-urea	pdr pure	
Diphenyl	pure	
Diphenyl-guanidine	2 10	o o
Dithio acids, salts of	pure	
Di[illegible] amines	pure	
D[illegible]	as is	
D[illegible]	as is	
D[illegible]	as is	
D[illegible] Cleanser (prop.)	as is	
D[illegible] (prop.)	1	aq
D[illegible] lakes and toners	pdr pure	
Earth pigments	pure	
Elon fresh (prop.)	0.5	aq
E[illegible] hydrochloride	pdr pure	
Enamel (controls)	as is	
E[illegible]	pdr as is	
Ep[illegible] line	1	o.o.
E[illegible]	as is	
E[illegible] reagent	2	aq
Essential oils (controls)	1	alc.
E[illegible]	pure	
E[illegible] gums	pure	
Ether	60	o
Ethyl acetate	pure	
Ethylaminobenzoate	5	pet
Ethylenediamine	10	org. solvent
Ethylene dichloride	50	o.
Ethylene dichloride	0.1	alc.
Ethyl mercury chloride	0 5	aq
Ethyl mercury phosphate	0 5	aq.
Eucalyptus, oil of	1	alc
Eugenol	10	almond oil
Eura ointment (prop.)	as is	
E[illegible] lotions, cosmetics, shadows	as is	
Fats, oil of	5	pet
Fenchyl alcohol	pure	
Fennel, oil of	1	alc.

(Continued)

SUBSTANCES, CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTS (Cont.)		
Bismuth, metallic (scrapings)	as is	
Bismuth oxychloride	5	pet.
Bismuth subnitrate	25	pet.
Bismuth subsalicylate	14	o.o.
Black Flag (prop.)	pdr as is	
Black Flag (prop.)	liquid 25	o.o.
Black rouge	as is	
Bleaching powder (controls)	10	aq
Bluing	as is	
Bon Ami (prop.)	1	aq
Borax	sat. sol.	aq
Boric acid	pdr pure	
Boric acid ointment, U.S.P.	as is	
Borocaine	1	aq
Brake Fluid (prop.) (controls)	as is	
Brass, metallic scrapings	as is	
Brass polish	10	aq
Brass weldings, scrapings	as is	
Brazil nut	as is	
Brazil wood (redwood)	as is	
Brilliant cresyl blue BB(L)-877	pure	
Brillo (prop.)	as is	
Bromo acid 768*	pure	
Bronze liquid paint	as is	
Burow's solution	10	aq
Butesin	1	alc.
Butesin picrate ointment (prop.)	as is	
Butyl acetate	pure	
Butyl alcohol	pure	
Butyric acid	1	aq
Cade, oil of	5-10	pet.
Cadmium orange	pure	
Cadmium red, deep	pure	
Cadmium red, light	pure	
Caffeine	1	aq
Caladryl (prop.)	as is	
Calcimine	as is	
Calcium arsenate	pdr pure	
Calcium carbonate	3	aq
Calcium chloride	2-10	aq
Calcium fluoride	0.5	aq.
Calcium hydrate	0.125	aq
Calcium nitrate	10	aq
Calcium oxide	10	aq.
Calcium phosphate	10	aq.
Calcium sulfide	1	aq
Calmitol ointment (prop.)	as is	
Calomel	pdr pure	
Camomile, oil of	25	c.o.
Camomile, oil of	25	pet.
Camphor	pdr pure	
Camphor ice (prop.)	as is	
Camphor oil of	10	pet.
Camphor spirits of	as is	
Canada balsam	as is	
Cantharides, tincture of	1	alc.

Capsicum, tincture of	1	alc.
Caraway seed, oil of	25	c.o.
Caraway seed, oil of	1	alc.
Carbazole	pdr pure	
Carbon	as is	
Carbon disulfide	60	o.o.
Carbon paper	as is	
Carbon tetrachloride	pure	
Carborundum	as is	
Carbowax (polyethylene glycols)	as is	
Cardamon	as is	
Carrot	as is	
Cashew nut shell oil	3-5	alc.
Cassia, oil of	1	alc.
Cedar wood	as is	
Cement (controls)	as is	
Ceresin	pure	
Charcoal	as is	
Chestnut, extract of	10	aq.
Chicken fat oil	pure	
Chloral hydrate	10	aq
Chloramine	0.5-1	aq
Chlorbenzene	5	o.o
Chloretone	2	alc
Chlorinated lime	2-10	aq.
Chlorinated naphthalene	pure	
Chloroform	40	
Chloroplatinic acid	1	aq
Chlorpromazine*	25	aq.
Chocolate	as is	
Chrome-alum	as is	
Chrome metal	as is	
Chromic acid	0.5-1	aq.
Chromium chloride	2	aq.
Chromium potassium sulfate	10	aq
Chromium sulfate	2	aq.
Chrome yellow	pdr pure	
Chrysarobin	0.03	pet.
Chrysoidin brown	pdr pure	
Cinnabar	3	pet
Cinnamic acid	5	pet.
Cinnamon	pdr as is	
Cinnamon, oil of	5	
Cinnamylic acid	5	pet
Citric acid	1	aq
Citronella	as is	
Cleansing fluids, inflammable (prop) (controls)	60	o.
Cleansing fluids, noninflammable (prop.) (controls)	as is	
Cleansers (organic solvents) (controls)	50	o.
Cleansers (powders) (controls)	1	aq
Clorox (prop.)	3	aq
Clothing and clothing materials	as is	
Cloves	pdr as is	
Cloves, oil of	25	c.o.
Cloves, oil of	1	alc.

(Continued)

SUBSTANCES, CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING (Cont.)

CN (prop.)	1 10	aq
Coal tar, crude*	5-10	pet.
Cobalt chloride	2	aq.
Cobalt oxide	pure	
Cobalt powder (nickel free)	as is	
Copper sulfate	5	aq
Cocaine	1	aq.
Cochineal natural 932	10	aq
Cocoa	as is	
Cocobolo wood	as is	
Coconut, oil of	pure	
Codeine sulfate	1	aq.
Cod fish oil	pure	
Cod liver oil	as is	
Coffee	pure	
Coffee, oil of	pure	
Collodion	as is	
Colza oil	as is	
Copal	pure	
Copper chloride	1	aq.
Copper cyanide	pdr pure	
Copper scrapings	as is	
Copper sulfate	5	aq
Coriander oil of	1	alc.
Cosmetics, (controls with hair tonics etc., cuticle softeners, etc., which may be primary irritants)	as is	
Cotton seed oil	pure	
Crayons	as is	
Creosote	10	o o.
Cresol	0.5-1	aq
Crude oil	as is	
Crystal violet 681	2	aq
Cumaron	pure	
Cutch	pure	
Cuticle remover (controls)	as is	
Cutting oils (controls)	as is	
Cyclohexanol	50	o.o.
Dacron	as i	
Dama[illegible]	pure	
[illegible]	5	acet.
[illegible]	50	o o.
[illegible] (Ger prop. name [illegible] turpentine substitute)	50	o.o
Denatured alcohol (controls)	as is	
Deodorants	as is	
Depilatories (controls)	as is	
Dermatol (Ger prop. dusting powder)	pure	
Dextrin	50-80	aq
Diacetylamidoazotoluol	2	pet.
Dianisidine	pure	
Diazonium salts	1	pet.
(Sym) Di beta naphthyl paraphenylene diamine	pure	hlor
Dichlorbenzene†	5	alc.
Dichlorbenzidine	5	

Dichloronitro benzene		10	aq.
Diethylamino—ethanol		1	aq.
Diethylene glycol		10	aq.
Digalloyltrioleate		3.5	pet.
Dihydrostreptomycin		5	aq.
Diiodohydroxyquinoline		3	pet.
Dimethyl amine		pure	
Dimethyl aniline		10-25	o.
1 2-4 dichloronitrobenzene		1	acet.
1-4-2 dichloronitrobenzene		1	acet.
1-8 dihydroxy-anthranol		0.1	pet.
1-8 dihydroxy-anthraquinone		0.5	alc
1-8 dihydroxy-anthraquinone		0 5	alc.
1-4 dihydroxy-anthraquinone		0 5	alc.
1-2-4 dinitrochlorobenzene		1	acet.
Dinitrocresol		5	chlor
2-4 dinitrophenol		10	aq.
Dinitrotoluol		sat.	alc.
Di-orthotolyl guanidine	pdr	pure	
Di-orthotolylthio-urea	pdr	pure	
Diphenyl		pure	
Diphenyl-guanidine		2 10	o
Dithio acids, salts of		pure	
Ditolyl amines		pure	
Doral		as is	
Dusts		as is	
Dust oil		as is	
Dutch Cleanser (prop.)		as is	
Duz (prop.)		1	aq
Dyes, lakes and toners	pdr	pure	
Earthy pigments		pure	
Elon, fresh (prop.)		0 5	aq
Emetine hydrochloride	pdr	pure	
Enamel (controls)		as is	
Eosin	pdr	as is	
Ephedrine		1	o.
Erythrosine		as is	
Esbach reagent		2	aq
Essential oils (controls)		1	alc.
Ester		pure	
Ester gums		pure	
Ether		60	o.
Ethyl acetate		pure	
Ethylaminobenzoate		5	pet.
Ethylenediamine		10	org solvent
Ethylene dichloride		50	o.
Ethylene dichloride		0.1	alc.
Ethyl mercury chloride		0.5	aq
Ethyl mercury phosphate		0.5	aq.
Eucalyptus, oil of		1	alc
Eugenol		10	almond oil
Fenax ointment (prop.)		as is	
Eye lotions, cosmetics, shadows		as is	
Fagi, oil of		5	pet
Fenchyl alcohol		pure	
Fennel, oil of		1	alc.

(Continued)

SUBSTANCES, CONCENTRATI[illegible] [illegible]CLES TO BE USED
PATCH TESTING (Cont.)

Ferric chlorid[illegible]	2	aq
[illegible]	as is	
[illegible]	10	aq
[illegible]	10	aq
Fertilizers, most commercial preparations (controls)	as is	
Fixatif	as is	
Flavoring oils (controls)	2	alc.
Flit (prop.)	25	o.o
Floor wax (controls)	10	o.o.
Flour all kinds	as is	
Flour bleaches (controls)	as is	
Flowers, fresh, dry artificial (controls)	as is	
Fluorene	pure	
Fluorescein	1	alc.
Flux aluminum	as is	
Flux iron	as is	
Foods, any kind (except rinds of certain fruits, spices, mustard, etc.)	as is	
Formaldehyde	5	aq
Formic acid	1	aq.
Fowler s solution	as is	
Fresh (prop.)	as is	
Fruit, citrus, peel (controls)	as is	
Fuchsin	*10*	aq
Furfural	pure	
Furniture polish (controls)	10	o.o.
Furs, any dyed, natural	as is	
Fustic (yellow wood)	pure	
Fustic (yellow wood)	sat.	aq.
Gallal te	as is	
Gasoline, regular ethyl	60	o o.
Gentian violet	2	aq.
Ginger	pdr pure	
Ginger, oil of	25	c.o.
Glass Wax (prop.)	10	o.o.
Glue	as is	
Glycerine	pure	
Glycerine oil	as is	
Gold chloride	2	q.
Gold Dust (prop.)	as is	
Gold sodium thiosulfate	0.5	aq
Grapefruit peel oil (controls)	pure	
Graphite	as [illegible]	
Greases	as is	
Grease solvents, most proprietaries (control)	as is	
Guanidines	pure	
Gum arabic	as is	
Gun grease	as is	
Gunpowder	as is	
Gutta percha	as is	
Gutta siac (a rubber)	as i	
Hair all kinds, natural dyed	as is	
Hair lacquers	as is	
Hair tonics, lotions (controls)	as is	
Hat glazing sizing or lacquers for (controls)	as is	

Hempseed oil	as is	
Henna, Egyptian	as is	
Henna, white	as is	
Hexahydrophenol	50	o.o.
Hexalin ($C_6H_{11}OH$)	50	o.
Hexamethylene tetramine	pur	
Hexylresorcinol	as is	
Histamine (acid phosphate)	0.1	aq.
Homatropine	1	aq.
[illegible]	1	aq.
[illegible]	1 2.5	pet.
[illegible]	0.2	aq.
[illegible]	10	aq.
[illegible]	5	aq.
Hydroterpene	50	o.
Hydroxymercurichlorphenol	0.5	aq.
Hydroxymercuricresol	0.5	aq.
Hydroxymercurinitrophenol	0.5	aq.
Hypnotics	as is	
Ichthyol	5-10	pet.
Indigo	10	aq.
Indole	sat.	aq.
Inecto A (prop. hair dye)	as is	
Inecto B (prop. hair dye)	as is	
Ink eradicators (controls)	as is	
Inks	as is	
Insect sprays (controls)	50	
Iodine crystals	0.5	pet.
Iodine crystals	1	alc.
Iodine, tincture of, U S P (Do not cover)	as is	
Iodobismitol (prop.)	as is	
Iodoform	25	pet.
Iridium chloride	10	aq.
Iron chloride	2	aq.
Iron, metallic scrapings	as is	
Iron sulfate	10	aq.
Istizin, 1-8 dihydroxyanthraquinone	0.5	alc.
Javelle water	10-20	aq.
J O Roach Powder (prop. insecticide)	as is	
Juniper oil of	25	c.o.
Juniper oil of	1	alc.
Karbolineum (Ger. prop. wood preservative)	50	o.o.
K R It (prop. insecticide)	as is	
Kerosene	60	o.o.
Lac dyes	50	pet.
Lacquer (controls)	as is	
LaFrance (prop.)	as is	
Lakes	50	o.
Lanolin	as is	
Lard	as is	
Larocaine	1	aq.
Larvex (prop.)	10	o.o.
Latex	as is	
Laurel oil of	25	c.o.
Lava soap (prop.)	1	aq.
Lavender oil of	1	alc.

(Continued)

SUBSTANCES, CONCENTRATIONS AND VEHICLES TO BE USED FOR PATCH TESTS (Cont.)

Lead arsenate	pure	
Lead arsenate	5	aq.
Lead azide	pure	
Lead chloride	pure	
Lead styphnate	pure	
Lead subacetate	0.2	aq
Lead sulfide	2	aq
Lead, white	as is	
Leathers, natural tanned, dyed, imitation	as is	
Lemon, oil of (controls)	1	alc.
Licorice	as is	
Lifebuoy soap (prop.)	5	aq.
Lighter fluid	50	o.o.
Lime burnt	10	aq
Lime, slaked (controls)	as is	
Linalool	1	alc.
Linseed oil	as is	
Lipstick*	as is	
Liquor carbonis detergens	10	pet.
Liquor sesquichlorati	10	aq.
Listerine (prop.)	10	aq.
Lithol red 189 as lakes and toners	as is	
Logwood	sat.	aq.
Lubricating oils (controls)	as is	
Lugol's solution, U.S P	50	aq.
Luminal (prop.)	as is	aq
Lysol (prop.)	1	aq
Mace, oil of	1	alc.
Machine oil (controls)	50	o.o.
Manganese chloride	2	aq.
Manganese oxide	pure	
Maroon 677 (partly impure magenta)	as is	
Mascara	as is	
Mastic	pure	
Mastisol (Ger prop. collodion-like substance)	as is	
Melissa, oil of	1	alc.
Menthol	1	pet.
Mentholatum (prop)	as is	
Mercaptens	pure	
2 Mercaptobenzothiazole	1	pet.
Mercurochrome	2	aq.
Mercury bichloride	0.1	aq
Mercury fulminate	pure	
Mercury oxycyanate	0.1-0 2	aq.
Mercury white ammoniated	5-10	pet.
Mercury yellow oxide of	5	pet.
Merthiolate, tincture of (prop.)	as is	
Mesquite wood	as is	
Metals, pure alloys	as is	
Metaphen	0 5	alc.
Metastal Ointment (prop.)	as is	
Metatoluylene diamine	pure	
8-Methoxypsoralen	1	
Methyl acetate	pure	pet.
Methyl acrylate	as is	
Methyl alcohol	pure	

Methyl aniline	10-25	o.o.
Methyl benzoate	1	aq.
Methyl heptin carbonate	0.1	alc.
Methyl orange 142	5	aq.
Methylprotocatechuic aldehyde	10	pet.
Methyl salicylate	2	o.o.
Methyl violet-680	2	aq.
Methyl violet, as lake	as is	
Metol (prop.)	5	aq.
Michler hydrol	5	alc.
Mineral colors or pigments	as is	
Mineral oil	as is	
Mint	as is	
Mirbane oil	25	o.o.
Mistol (prop.)	as is	
Monobenzylether of hydroquinone (agerite, alba) (prop.)	1.5	alc.
Monobenzylether of hydroquinone (agerite, alba) (prop.)	1.5	pet.
Monobenzyl para-amino-phenol	pure	
Monochlor-benzene	5	o.o.
Morphine	1	aq.
Moth flakes	as is	
Mouth washes	as is	
Mucilage	as is	
Mum (prop.)	as is	
Mustard, oil of	1	alc.
Mycostatin ointment (prop.)	as is	
Naftalan (Ger. prop.)	10	pet.
Nail polish	as is	
Naphtha	50	o.o.
Naphthalic acid	1.5	aq.
Naphthalene	pure	
2 Naphthalene 1-sulfonic acid azo-beta-naphthol	as is	pdr
Naphthenol	50	o.
Naphthol yellow	pure	
Naphthylamine	2	alc.
Neoarsphenamine	1	aq.
Neomycin ointment (prop.)	as is	
Nickel nitrate	3	aq.
Nickel sulfate	5-10	aq.
Nicotine salicylate (do not test with base)	5	aq.
Nigrosine	pure	
Nile blue	pure	
Nitric acid	2-3	
Nitrobenzol	10-25	aq.
Nitrophenol	5	o.
Nitroso-dimethyl aniline	1	chlor.
Novocaine (prop.)	2	alc.
N[illegible] (prop.)	as is	aq.
Nupercaine (prop.)	1	pet.
Nutgalls, roasted	as is	
Nutmeg, oil of	25	o.o.
Nylander reagent	as is	
Nylon	as is	
Oakum	as is	

(Continued)

toma in man is rare or perhaps rarely recognized. The clinical appearance is remarkably constant. The lesion is present at birth or appears soon afterward as a pink, red or yellow papule or small plaque *on any part of the* skin but with predilection for the extremities, especially the wrist. For a few weeks or months the lesion may increase in size until it reaches the final state as a round or oval, well-circumscribed, reddish to light brown, slightly elevated plaque 1.5 cm. in *diameter (Fig. 23).* The rounded surface may *be smooth or* have an orange skin appearance and a rubbery infiltration is palpable. At intervals of several weeks the tumor spontaneously or after irritation *suddenly swells,* becomes red and

Fig 23.—Solitary mastocytoma ri ht lbow (Courtesy of M rshall, J ... South African M J 31 847-876 Aug 31 1957.)

may have superficial vesicles on its surface. Dermographism of the unaffected skin is demonstrable in some cases. Diagnosis *ultimately* rests on *showing a mast* cell infiltrate in the dermis. Many solitary mastocytomas are probably dismissed as moles or banal nevi which in their quiescent state they closely resemble.

The *flushing phenomenon* was noted only once *before* in a patient with solitary mastocytoma. Similar episodes have rarely been reported as occurring in urticaria pigmentosa.

Visceral lesions may be observed with any cutaneous variety of mastocytosis except possibly in solitary mastocytoma in which positive proof of visceral lesions still is lacking. Presence *of visceral lesions in no way alters* prognosis for the worse.

The transitory cutaneous phenomena that characterize

Phenolphthalein, white or yellow	pdr	2	alc.
Phenyl-alpha-naphthylamine		pure	
Phenyl-beta-naphthylamine		pure	
Phenyl glycine		pure	
Phosphorous trisulfide		0 5	pet.
Photographic developers		5	aq.
Phthalic acid		1 5	aq
Phthalic anhydride†		1	alc.
Picric acid		1 5	aq.
Picryl chloride†		1	acet.
Pigments, for artists, etc		as is	
Pine oil (controls)		pure	
Pine wood		as is	
Pitch (just apply) (no covering)		as is	
Plants† fresh, dry any part of (controls)		as is	
Plant oils (commercial preparations for testing are available)		as made	
Plexiglas		pure	
Plaster of paris		as is	
Plaster wall		as is	
Plastibase (prop)		as is	
Plastics		as i	
Plastic (shoe) box toe		as i	
Platinum chloride		10	aq.
Poison ivy extract—8% solids†		0 1	acet.
Polishes, commercial (prop)		as is	
Polyvinyl chloride (material)		as is	
Pontachrome blue black R 202		pure	
Pontacyl black (similar to 246)		pure	
Pontamine black 501		pure	
Pontamine blue-406		pure	
Pontamine diazo black-401		pure	
Pontamine fast orange S		pure	
Pontocaine hydrochloride		2	e o.
Poppy seed oil		as is	
Potash		10	aq
Potassium acetate		10	aq
Potassium arsenite, U S P		as is	
Potassium bichromate		0 5-1	aq
Potassium bromate		6	aq
Potassium bromide		1-6	aq.
Potassium bromide		25	pet.
Potassium carbonate		0 7 3	aq.
Potassium chlorate		10	aq.
Potassium chloride		5-10	aq.
Potassium chromate		0 5	aq
✓Potassium citrate		10	aq
Potassium ferricyanide		10	aq.
Potassium ferrocyanide		10	aq
Potassium hydroxide		0 5	aq
Potassium iodide		3-6	aq.
Potassium iodide		25	pet.
Potassium nitrate		25	aq
Potassium permanganate		1	aq
Potassium persulfate (should be freshly made)		2 5	aq
Potassium salicylate		as is	

(Continued)

Substances, Concentrations and Vehicles to Be Used in Patch Testing (Cont.)

Powder cleansing scouring (controls)	as is	
Powder face, bath	as is	
Pragmatar Oint.* (prop.)	as is	
Primrose expressed juice of fresh plant†	25	aq.
Primrose, leaf†	as is	
Procaine (base)	1	pet.
Procaine hydrochloride	1	pet.
Propylene glycol	10	aq.
Protein extracts, foods, plants bacteria	as is	
Pyredine	30	o.o.
Pyrethrum, milled powder	as is	
Pyrethrum, tincture of	as is	
Pyribenzamine ointment (prop.)	as is	
Pyro	as is	
Pyrogallol	3	aq
Qualatum (prop.)	as is	
Quercitron	pure	
Quinine* [illegible]	1	aq
[illegible]	1	aq
[illegible]	25	pet.
[illegible]	0.5	alc.
Quinolor compound ointment (prop.)	½ strength (diluted with pet.)	
Quinosol	0.2-0.5	dext.
Rapeseed oil	pure	
Raw umber	as is	
*Red moss	as is	
Resins† (controls see plants)	as is	
Resorcin (controls)	3	aq
Rhodamine B 749 lakes and toners of	as is	
Rhodine	as is	
Rhodium chloride	10	aq.
Rice oil	as is	
Rockwood	as is	
Rose, oil of	25	pet.
Rose oil of	1	alc.
Roux	as is	
Rubber rubber products	as is	
Rubber (synthetic)	as is	
Rusci, oil of	6	pet
Rye, oil of	pure	
Safranine O 841	pure	
Sal ammoniac	3	aq.
Salicylic acid	5-10	pet.
Salol	as is	
Salves (prop.) (controls)	as is	
Sangajol (Ger prop. name for turpentine substitute)	30	o.o.
Santal, oil of	1	alc.
Sassafras, oil of	2	o.o.
Sassafras, oil of	1	alc
Scalp lotions (controls)	as is	
Scopolamine	1	aq
Selsun (prop.)	5	aq.
Sensol	as is	
Shampoos (controls)	1 3	aq

Shellac (controls)	as is	
Shoe dyes (controls)	50	o.o.
Shoe polishes (controls)	60	pet.
Silver amalgam	as is	
Silver metallic, scrapings	as is	
Silver nitrate	5	aq.
Silver nucleinate	5	aq.
Silver paint	as is	
[illegible] (prop.)	as is	
Skatol	sat.	aq.
Skolex (prop)	as is	
Smokeless gunpowder	as is	
Soaps (controls)	1 3	aq
Soap, tincture of green	5	pet.
Soap, tincture of green	2 5	alc.
Sodium arsenate	10	aq.
Sodium benzoate	20	aq
Sodium bicarbonate	10	aq.
Sodium bichromate	3	aq.
Sodium bromide	25	pet.
Sodium carbonate	3-10	aq.
Sodium chloride	10	aq
Sodium fluoride	0.5	aq.
Sodium fluorosilicate	0.5	aq
Sodium hydroxide	0 5	aq
Sodium hypochlorite	10	aq.
Sodium hyposulfite	1	aq
Sodium meta-[illegible]	1	aq.
Sodium metabisulfite	2	aq.
Sodium oleate	1	aq.
Sodium para-aminobenzoate	1	aq
Sodium salicylate	1	aq
Sodium stearate	1	aq
Sodium sulfate	5	aq
Sodium sulfide	2	aq.
Sodium sulfite	1	aq
Sodium thiosulfate	1	aq.
Soluble blue 325	pure	
Spearmint, oil of	1	alc.
Spermaceti	pure	
Spic and Span (prop)	1	aq.
Spirits of ether	as is	
Spray spray (auto) (controls)	as is	
Stamps	as is	
Starch	as is	
Stearic acid	1	aq
Steel wool	as is	
Sterosan ointment or cream (prop)	as is	
Streptomycin	2.5	aq
Sudan III 223	5	o.o.
Sugar	as is	
Sulfaphenazone	5	aq
Sulfogene carbon	pur	
Sulfogene golden brow	pur	
Sulfonamides*	pdr as is	
Sulfonamides*	5	pet.

(Continued)

SUBSTANCES, CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING (*Cont.*)

Sulfonamides (prop. topical remedies)	as is	
Sulfonated oils	pure	
Sulfosalicylic acid	pure	
Sulfur (precip. or sublimed)	5 10	pet.
Sulfur monochloride	1	carbon disulfide
Sulfuric acid	5	aq.
Sulfurous acid	1 2	aq.
Sumac leaves, fresh or dry	as is	
Sunflowers, oil of	as is	
Sun protective cream (prop.)	as is	
Tallow	as is	
Tannic acid	1	aq.
Tar paper*	as is	
Tar solution of, N F	10	aq.
Tars (No covering! Simply apply)	as is	
Tartar emetic	3	aq.
Tartar emetic, powder	as is	
Tartrazine yellow-640	pure	
Terpineol	pure	
[illegible]	50	o.o.
[illegible]	30	o.o.
[illegible]	5	pet.
[illegible]	1	alc.
[illegible]	pure	
Tetryl	sat.	ether
Thephorin ointment (prop.)	as is	
Thioglycerin	5	aq.
Thioglycolic acid	10	aq (pH4)
Thiosinamine	10	alc.
Thioureas	pure	
Thiuram sulfides	pure	
Thyme, oil of	*25*	c.o.
Thyme, oil of	25	alc.
Thymol	1	pet.
Thymol iodide	*25*	pet.
Tide (prop.)	1	aq
Tin chloride (stannous)	10	aq
Tin foil	as is	
✓Tincture veratrum viride, U.S P	as is	
Tintex (prop.)	as is	
Tobacco extract (controls)	as is	aq
Tobacco leaf (controls)	as is	
Toilet waters*	as is	
Toluidin	10-50	o
Toluol	50	o.o.
Toners	pdr pure	
Toni home permanent (prop.)	50	aq
Tooth pastes, powders (controls)	as is	
Tragacanth	1	aq
Triacetin	pure	
Trichlorethylene	50	o.o.
Trichlortoluol	50	o.
Trichophytins (controls)	undil.	
Tri-ethanol amine	1	aq.
Tri-nitro-anisol	0.01	chlor
1-2-4 trinitrobenzene†	1	acet.

1,3,5 trinitrobenzene	1	acet.
Trinitrotoluol	sat.	alc.
Trisodium phosphate	2	aq
Trypan blue 477	pure	
Trypan red 438	pure	
Tryparsamide	6	aq.
Tuberculins (controls)	undil.	
Tumenol (prop.)	5	pet.
Tumenol ammonium (prop.)	6	pet.
Turmeric	pure	
Turpentine (controls)	25	
Tutocaine	2	aq
Typewriter ribbon	as is	
Tyrosine	sat.	aq
Ultramarine blue	as is	
Undecylenic acid cream (prop.)	as is	
Uranium chloride	10	aq
Urea	10	aq
Uric acid	1	aq
Vanilla, oil of	25	alc
Vanillin	10	pet.
Varnish (controls)	as is	
Varnolene	60	o.
Venetian red	pure	
Vert emeraude	pure	
Victoria blue	pure	
Vinegar	as is	
Vinyl resins	pure	
Vioform ointment or cream (prop.)	as is	
Walnut, oil of	pure	
Water colors	as is	
Wave sets (prop.)	50	aq
Wax, floor (controls)	50	o.
Waxes, polishing in general (controls)	as is	
Wheat, oil of	as is	
Whitfield's oint. N.F.	as is	
Windex (prop.)	50	aq
Window sprays	as is	
Wintergreen, oil of	1	alc.
Witch hazel	as is	
Woods, natural, painted, stained (controls)	as is	
Wormwood, oil of	25	c.o.
Xeroform	25	pet.
Xylol	50	o.
Yellow ochre	pure	
Zinc chloride	2	aq.
Zinc oxide	pure	
Zinc chromate primer (after drying)	as is	
Zinc peroxide	pure	
Zinc stearate	pure	
Zinc sulfate	10	aq.
Zinc brie	as is	
Zonite (prop.)	1	aq.

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1 TREATMENT AND PREVENTION

A. Endocrine Therapy

Observations on Steroid Therapy in Psoriasis in 14 severely afflicted patients are reported by A. Girdwood Fergusson and W. A. Dewar (Glasgow) All except 1 were treated with daily intramuscular injections of adrenocorticotropic hormone, 100-150 mg daily for 2½-28 days Several received supplementary doses of prednisolone in varying amounts. Treatment was discontinued in 3 patients because of complications. Steroid therapy is not satisfactory for psoriasis even though initially there may be improvement in chronic cases and exfoliative states, arthritic symptoms may be benefited, and severe relapses are uncommon. Steroid therapy may save clothing and bed linen but its effect is merely palliative. This advantage is offset by the expense of treatment and necessity for carrying out laboratory procedures while the steroids are being used.

Greatest duration of treatment in this series was 2 years 8½ months but fairly high sustaining doses were required (50 mg ACTH daily) It is believed steroids are indicated in cases complicated by exfoliative changes and arthritis

► [We] agree that today neither corticotropin nor corticosteroids are the agents of choice in management of psoriasis unless the eruption is spreading rapidly or the disease is in a generalized exfoliative state. Ordinarily large doses of these hormones are required to bring the disease under control, e.g. 20-30 mg ACTH intravenously daily for several days, intramuscularly in the doses given by the authors or 200-500 mg. cortisone or its equivalent orally Once the psoriasis is under control, it is possible to gradually reduce the doses to 100 mg or slightly less and still maintain general improvement Stopping these drugs results in flare up of the disease As these drugs are being given systemically, topical therapy should be used simultaneously with the hope of maintaining any improvement achieved with the corticosteroid.

However with the development of newer analogues of cortisone it appears entirely possible that this situation may change For example, triamcinolone appears to be more effective (in equivalent doses) in the management of psoriasis than the other corticosteroid drugs. Doses as small as 8-16 mg daily may produce striking improvement in psoriasis vulgaris and not only in erythrodermic cases or those associated with arthritis Maintenance doses of triamcinolone which satisfactorily suppress the disease are so moderate in some cases that its administration may be continued with relative safety when topical therapy is insufficient In addition to this

( ) Brit J Dermat 69 17-44, February 195

seemingly favorable effect of triamcinolone, when one considers the apparent lack of effect of this drug on sodium and potassium metabolism and water balance, one cannot help but appreciate the progress that has been made in this field and look with anticipation for what the future may bring.—Eds.]

Sclerema Neonatorum Recovery with Cortisone. Ian G Wickes[2] reports a case

Boy aged 5 days, was thin, wizened and immobile. Weight was 5 lb. 2 oz. and temperature was too low to record. The skin over the whole body was bound tightly to the underlying tissues and could not be picked up from them. The knees and hips were flexed and could not be extended. The cheeks and lips felt woody and the chest expanded poorly Fine crepitations were audible over both lung fields.

Therapy was started at once with 25 mg cortisone 3 times daily and 50 mg tetracycline twice daily given by tube. Oxygen was given and the infant was fed breast milk by tube because he was unable to nurse Within a few hours the skin seemed a little looser, thereafter steady improvement was noted. The temperature was 97 F on the 2d treatment day and normal on the 3d day He was able to suckle from the breast for the first time on the 2d day The arms and chest became normal by about the 4th day but slight woodiness of the tissues of the lower extremities persisted for about 1 week. Cortisone was reduced to 50 mg daily on the 6th day and discontinued on the 10th. At that time, weight was 6 lb 3 oz. Full recovery occurred and there was no relapse.

The infant received a total of 570 mg cortisone. This probably was unnecessarily large but the situation was desperate No harmful effects were observed

In recent years there have been 6 other similar case reports of rapid recovery with ACTH or cortisone No failure in treatment of sclerema neonatorum with steroids has been reported. Nearly all patients treated with ACTH or cortisone also have received antibiotics Improvement however seemed to coincide with the hormone therapy

► [*Neither the corticosteroids nor corticotropin are ever given credit for "curing" a disease, and thus Wickes uses the expression "recovery with cortisone" to describe the beneficial effects in these cases. If not curative this hormone undoubtedly plays an important role in enabling other corrective mechanisms in these infants to become operative, or perhaps cortisone keeps these infants alive long enough for the disease to run its course—fortunately a favorable one.—Eds.*]

Fractionation of 17 Ketosteroids in Patients with Exfoliative Dermatitis Following Long Term Cortisone Therapy Tauno Putkonen S Pesonen, Katri Rehtijarvi and R. Kristoffersson[3] (Helsinki) abruptly discontinued hydrocortisone therapy in 3 men aged 29-54 with chronic generalized

(2) Arch. Dis. Childhood 31 419-421, October 1956.
(3) Acta dermat.-venereol. 36 450 462, 1956.

exfoliative dermatitis to observe the consequences Fractionation of 17-ketostero ds was carried out immediately before stopping treatment, and in the middle and at th end of the period between treatments Interruption of treatment was followed in each by rapid aggravation of the dermatitis. In the oldest patient who had received hormone therapy for 27 months and whose maintenance dose was 120 mg hydrocortisone, such severe oozing of the skin developed that plasma proteins declined within 10 days from 7.89% to 5 15% The patient lost 6 kg body weight during 14 days.

Th youngest patient who had been under treatment for 11 months and had a maintenance dose of 220 mg hydrocor tisone showed decline in plasma proteins from 6 86% to 6.17% n the same period. Because of inflammatory edema, his weight increased 4 kg during the first 4 days without treatment, but oozing of the skin resulted n loss of 3 kg body weight during the last 10 days without hydrocortisone

Interruption of treatment was best tolerated by the pa tient aged 44 who had recei ed the hormone for 26 months but had maintenance dose of only 60 mg Plasma protein lev l nd body weight rema ned unchanged although treat ment was interrupted for 20 days

Urinary excretion of 17 ketosteroids and dehydroepian drosterone was low in all during therapy When treatment was topped, n all there was some increase n excretion of 17-ketosteroids, with the most rapid and pronounced increase occurring in 1 patient w th the lowest maintenance dose In separate determinat ons of dehydroepiandrosterone originating in the adrenal cortex, this patient showed the greatest ncrease after d scontinuation of treatment. Judg g from this his adrenal cortex still retained some secretory capacity although he had received hormone therapy for over 2 years The patient with the largest maintenance dose also was capable of ncreased excretion of dehydroepiandroster one during treatment interruption but no increase occurred in the patient who had least tolerance to cessation of treat ment. Apparently ad enocortical atrophy was most ad a ced in his case.

During hydrocortisone therapy adrenalectomized and or chiectomized patients ha e been noted to excrete in the urine 2 5 % of administered hormone in the form of 11-oxy 17 ketosteroids. Among the present patients, nearest approach

to this was observed in the one with the most advanced cortical atrophy During hydrocortisone treatment his rest fraction which contains the 11-oxy 17 ketosteroids was only 80% of the mean rest fraction of men in his age group but it decreased so much during the period of suspended treatment that the difference corresponded to 1 2% of his hydrocortisone dosage. The other 2 patients had still lower rest fractions during treatment and they did not change appreciably during cessation of treatment although 1 required nearly twice as large a dose of hydrocortisone as the first mentioned patient. Thus size of the rest fraction was not determined by size of the hydrocortisone dosage Rather the atrophy of the adrenal cortex appeared to have some influence on the rest fraction

Function of the testes was apparently depressed in the 3 patients because the combined excretion of 17 ketosteroids originating in the testes—androsterone and etiocholanolone—was low It did not increase during the nontreatment period even in patients who during that period were capable of increased excretion of dehydroepiandrosterone This suggests that regeneration of the testes is not as rapid as is that of the adrenal cortex

Androsterone and etiocholanolone behaved differently during treatment and after its cessation Maximum excretion of androsterone was noted during nontreatment whereas for etiocholanolone it was during treatment It has been found that in a hypophysectomized patient excretion of androsterone ceases completely but excretion of etiocholanolone increases somewhat The difference observed in excretion of androsterone and etiocholanolone in the present cases during hydrocortisone treatment and during suspension of treatment probably points to depressed hypophysial function

Many details observed in study of the different fractions of 17 ketosteroids still await definite explanation All conclusions, therefore must be accepted with reservation. The effect of stress on adrenocortical function also complicates the picture

► [This study vividly points out the extremely undesirable consequences that follow sudden withholding of systemic corticosteroid therapy At the same time, it shows that even after the *prolonged* administration of reasonably large doses of hydrocortisone, the adrenal cortex is still capable of taking over to some degree and that it is not atrophied to the point of inability to function.—*Eds.*]

Impetigo Herpetiformis Report of Three Cases and Discussion of Treatment with Adrenocorticotropic Hormone—Survey of 6 Years Cases in Literature. According to Eigill Hvidberg[4] (Finsen Inst Copenhagen) the disease is considerably more common in women than in men. Women often acquire the disease or a recurrence during or immediately after pregnancy Hypoparathyroidism and low serum calcium have been shown in several cases A striking proportion of women have a history of thyroidectomy In many some form of endocrine therapy is effective, whereas others respond to chemotherapy or reco er spontaneously In many cases therefore some form of endocrine imbalance appears to be the cause or a contributory cause, whereas in others, infection seems to be important etiologically

CASE 1—Woman, 30 had widespread impetigo herpetiformis that appeared shortly after delivery Her temperature was over 102.2 F for 4 day and there was no improvement with antibiotics, which were discontinued. Treatment with gonadotropic hormone (Antex) a total of 48,000 units over 8 days, resulted in complete clearing of lesions and disappearance of systemic symptoms.

CASE 2—Man, 65 had ecurrent impetigo herpetiformi for 18 months, with no improvement from treatment with antibiotics, human gamma globulin, male sex hormones, blood transfusions, ACTH and cortisone H died in state of erythroderma, and autopsy failed to gi any relevant information.

CASE 3—Woman, 34 had impetigo herpetiformis during a pregnancy 12 years ago. She was sterilized after another attack during the next pregnancy For the next 10 years she had minor attacks at each menstrual period. During the past years symptoms were increasing l severe, accompanied by generalized erythroderma. The effect from ACTH ppeared temporary but cortisone, Meticorten all antibiotics, gonadotropic hormone, estrogenic hormone, parathyroid hormone and calciferol were ineffecti e.

In ll 3 pat ents, th course of the d sease and morphology f the eruption were considered typical of impetigo herpetif rm Dysfunction of the parathyro d glands was not de tected n a y case a d infection did not appear to be at factor

Duri g the past 6 years 19 cases of impetigo herpetifor m ha been reported, ncluding the present 3 In 7 ACTH nd cortisone known to have been tried w th good esult in 2 nd doubtful effect n 2 thers It is nteresting that no harm esulted from use of these hormones, which know to d sem nate infection

[4] [W... onder ... hat might have been the effect of sulfapyridine, Proms Dermatologica 1 337 341, June, 917]

cetin* Diasone* or Dapsone* in Hvidberg's cases, if they had been tried. The editors in their combined experience have observed but 1 case, a Scottish woman (private patient of Dr Max Jessner) with impetigo herpetiformis. Apart from this case, we do not recall seeing any other in the New York Skin and Cancer Unit, in our private practices or at meetings that was *unhesitatingly* diagnosed as impetigo herpetiformis. This could be due to absence of such cases or to different criteria used for diagnosis. —Eds.]

Treatment of Ichthyosis Congenita Gravis with Cortisone *is recommended by H Hanssler*[5] *(Univ* of Tubingen) who reports the disease in 3 children (first third and fourth born) in the same family The parents are in good health and there is no history of consanguinity The second child boy 8 was healthy at birth and has no skin manifestations

CASE 1—Girl born in 1947 showed ichthyosis congenita gravis at birth. Large, polygonal horny scales covered the whole body The trunk shaped mouth protruded and was stiff the horny partly cracked lips could not be closed. The ears were small and deformed. Ectropion of the upper and lower eyelids was observed. The limbs were fixed in flexion. Death occurred on the 12th day

CASE 2.—Boy born in 1952, also showed the disease at birth. The face, body and extremities were covered with thick, horny masses, which were cracked in several places, with bleeding skin beneath. There was a cauliflower like malformation of otherwise small ear lobes. After vitamin A therapy (200 000 units/day) exfoliation of thick lamellae was seen and small areas of normal rosy skin appeared. Rapid loss of strength occurred in the 6th week of life, followed by death due to pulmonary edema.

CASE 3—Boy born in 1956 with the disease, was hospitalized 7 days after birth. The cutaneous manifestations were identical to those seen in the first born. Because of the fatal outcome of the disease in the other children cortisone was given (25 mg ¼ tablet 4×daily) for 3 weeks together with vitamin A (120,000 units/day) orally for the first 5 days. After 4 days, exfoliation of the large, horny lamellae was seen. The ectropion of the eyelids and horny thickening of the lips disappeared the limbs became more movable. After 3 weeks, the cortisone doses were reduced to 18.25 mg., ¼ tablet 3×daily Further reductions or substitution by prednisone, however produced immediate relapse with marked epithelial thickening and scaliness. At discharge on the 77th day after hospitalization, the child's body weight had increased by 2 080 Gm. the skin was normal and remained so despite discontinuation of cortisone for 8 days because of intervening encephalitis with fever and otitis media. When seen at age 11 months the child was completely normal.

Cortisone therapy may not only prevent fatalities but also cure ichthyosis congenita gravis, which previously was considered to be therapy resistant.

► [A remarkable result which warrants extensive trials in other cases —Eds.]

(5) Deutsche med. Wchnschr 82 1733-1734 October 1957

Experiences with Cortisone Treatment of Pemphigus are reported by W Matter[4] (Univ of Vienna) During the past 4½ years, 5 men and 11 women aged 29-85 with pemphigus vulgaris (9) pemphigus erythematosus (2) pemphigus mucosae (3) pemphigus foliaceus (1) and pemphigus vegetans (1) were treated with cortisone. Before beginning the cortisone therapy the disease had been present 90 months in the patient with pemphigus follaceus and in most patients 1-6 months. Initial doses of 300-600 mg or more daily (in a severe case 800 mg/day) were given. Doses were gradually reduced to a maintenance dose which varied between 150 and 25 mg/day

All patients showed marked moon facies and weight increase. Occasionally hyperpigmentation, hyperhidrosis, hypertrichosis, anomalies of menstruation and psychic changes were seen Steroid diabetes was observed in 4 tetanic seizures with hypocalcemia and hypoproteinemia occurred in 1

Reduction or discontinuation of cortisone therapy resulted in nea ly complete disappearance of side effects except weight increase, which yielded slowly Attempts to substitute cortisone with ACTH were not successful and regularly caused deterioration of the pemphigus.

Two patients died their deaths, however were not associated with the pemphigus or cortisone therapy (1 committed suicide the other died of senility) Of the 14 survivors 11 were able to resum work. Results of the cortisone therapy were therefo e, considered to be satisfactory

► [W also prefer oral corticosteroid therapy to ACTH injections for routine treatment. In principle, however ACTH therapy is just as efficient as cortisone therapy The author's failure with ACTH in pemphigus must be attributed to the fact that he attempted ACTH therapy after his patients had been on, probably prolonged, cortisone therapy Due to the suppression of secretory capacity of the adrenal cortex under corticosteroid therapy the transition from corticosteroids to ACTH should be made very slowly and gradually to give the adrenal cortices chance to recover and regain their capacity to respond to the stimulation by ACTH A sudden change to ACTH treatment usually leads to quick worsening in pemphigus and other chronic diseases

As far as oral therapy with cortisone analogues is concerned, further advance in reducing side effects hile maintaining therapeutic activity, has been made ith the development of triamcinolone (Aristocort® and Kenacort) and methylprednisolone (Medrol®) Triamcinolone, which has a fluoride atom in the 9 position and hydroxyl group in the 16 position, apparently does not cause patients to retain sodium and water and does not necessitate potassium supplements. Therefore, it appears that patients no longer hav to be maintained on low salt diet. In addition to this distinct

[4] Dermatologica 1 17 26, January 1957

advantage, 2 mg triamcinolone often has about the same therapeutic effect as 3 mg prednisone. Methylprednisolone also apparently has distinct advantages over the older steroids and 4 mg of this compound is equal to 5 mg prednisolone.—Eds.]

Treatment of Pemphigus with Corticosteroids Study of 52 Patients treated in the dermatologic wards of Bellevue Hospital is presented by Maurice J Costello Leon Jaimovich and Marvin Dannenberg[7] Of 50 whites 60% were Jews. Of the total patients 42 (81%) had pemphigus vulgaris 5 pemphigus foliaceus (Fig 1) 4 pemphigus ery



Fig. 1 —Pemphigus foliaceus, with bizarre pattern which is pathognomonic of the form and consists of polycyclic, imbricated plaques made up of crescentic flaccid bullae. (Courtesy of Costello, M J et al J A M A 165 1249-1255 Nov 9 1957)

thematosus and 1 pemphigus vegetans The sex incidence was about equal

The initial site of the pemphigus bullae was the mucous membranes of the mouth in nearly 55% of the patients The high incidence of this site is important in early diagnosis of pemphigus vulgaris Unruptured bullae are rarely seen on the oral mucosa because their thin walls are immediately ruptured by mastication and deglutition Persistent eroded patches of the oral mucous membranes especially in adult should prompt a thorough skin examination After exclusion of Vincent's infection desquamative gingivitis gangrenous stomatitis syphilis, vitamin deficiency and drug

(7) J.A.M.A. 165 1249 1255, Nov 9 1957

eruptions a patient with mucosal bullae should be considered as having pemphigus until proved otherwise. Early diagnosis and treatment may not only save the patient's life, but also prevent the distressing side effects of prolonged steroid therapy

To bring pemphigus under control as rapidly as possible, it was found efficacious to administer initial high doses of corticosteroids. If the urgency was great 25 units of corticotropin dissolved in 500-1,000 cc of 5% dextrose was administered intravenously daily or 40 units of repository corticotropin was given twice daily In less urgent but moderately extensive eruptions 20 (5 mg) tablets of prednisone were given daily until the disease was controlled. The dose was then gradually reduced to maintenance level which was usually 20-40 mg daily for several weeks or longer Most patients eventually required only 15-20 mg daily It was advantageous to augment this routine with 40 units of repository corticotropin intramuscularly once or twice a week. Several patients showed complications of steroid therapy and the disease recurred promptly after discontinuation of the drug In these cases, it was usually decided to re-treat the patient with corticosteroid in view of the hopeless prognosis with other forms of therapy

Pemphigus was treated in 270 patients at the Bellevue Hospital during the 40 years before introduction of steroid therapy The mortality was more than 90% in this group but in the steroid-treated group it was 33% This is probably a higher figure than that of other series reported because of the older age groups represented (78% were past age 50) the severity and extensiveness of the disease and the inadequate but prolonged corticosteroid therapy given many of the patients before hospitalization. Two of the steroid treated patients died of gastrointestinal hemorrhages, a complication which was not observed in the presteroid series

Corticosteroids were of greatest value in treating pemphigus vulgaris, of less value in pemphigus erythematosus and of little permanent benefit in pemphigus foliaceus. Few patients with pemphigus have been free from symptoms for 1 years or more without treatment.

We wish to stress the importance of giving adequate doses of corticosteroids from the very beginning to bring pemphigus vulgaris under control The initial dose ordinarily is between 300 to 1,000 mg. cortisone or its equivalent daily Once the disease is under control (and this does not

mean that all lesions have disappeared from the skin) the daily dose is *very gradually* reduced. Caution must be exerted not to lower the dose too *rapidly* because, *in event of an exacerbation of the disease*, returning to the previous effective dose is ordinarily ineffective to bring the eruption back under control, *considerably larger* doses are required. It is advisable that a competent internist be part of the therapeutic team, in particular when very large doses of corticosteroids are being administered and when corticosteroids have to be continued over a protracted period of time. —*Eds.*]

Treatment of Infantile Eczema with ACTH and Cortisone is discussed by Heinrich Klingenfuss[8] (Zurich) The good results of cortisone therapy were observed in 30 patients 23 of whom had infantile eczema (13 were improved and 9 cured) 3 seborrheic dermatitis and 4 neurodermatitis Dosage was 20-40-80 mg cortisone by mouth daily depending on the severity of the case. The therapy was continued 5-48 days (average 2 weeks) But for a slight weight increase in an infant of 6 months no side effects were noted.

The most significant advantages of cortisone therapy are fast-subsiding pruritus and diminution of edema and redness with the diseased areas gradually appearing dry and clean The greatest disadvantage is the almost regular recurrence of the eczema after discontinuation of therapy The results were most favorable in infants with eczema and in those with acute cases of seborrheic dermatitis and neurodermatitis they were less favorable in infants with localized lichenified plaques of subacute or chronic neurodermatitis.

In mild cases of infantile eczema, the topical application of 1-2% hydrocortisone ointment possibly combined with an antibiotic is indicated Because of slight absorption this treatment may be extended for several weeks without risk

In severe cases cortisone internally (40-60 mg/day) or Meticorten® (20-30 mg/day) are given Because of a possible masked infection an antibiotic (penicillin Aureomycin® or Terramycin®) should be added. To avoid side effects cortisone therapy should be limited to 3-4 weeks and gradually reduced. The best results are obtained by combining cortisone treatment with the classic method i e topical application of wet dressings lotions ointment bandages baths and proper diet (elimination of cow's milk cereals fish eggs potatoes tomatoes spinach oranges and chocolate)

(8) Ann. paediat. 188:226-246, April, 1957

In 2 cases of pustulosis varioliformis (Kaposi) cortisone therapy was ineffective.

► [W agree that in all except severe cases the older forms of treatment plus topical application of hydrocortisone usually suffice in infantile eczema. Topical treatment with hydrocortisone thus far (i.e., after years of experience) has not been found to produce systemic side effects, even after application to the highly permeable skin of infants. Therefore, it appears that its use can be continued indefinitely

For systemic therapy triamcinolone (Aristocort® or Kenacort) may ell prove to be the corticosteroid of choice because of its lesser side effects and because perhaps it is more effective in certain dermatoses than the older steroids.—Eds.]

Corticotropin and Cortisone Therapy in Dermatomyositis.
Without treatment, about 50% of patients with dermatomyositis d e within a few weeks to a few years. Some recover entirely others improve to some extent and remain stationary or become chronically crippled. In treating th s condition with cortisone and corticotropin varying results were obtained The most fa orable results occurred in patients with acute cases characterized by rapid onset with pyrexia, general toxemia, leukocytosis erythematous eruption and painful myopathy In these patients, cortisone and corticotropin can be lifesaving and the effect of treatment is often dramatic. These drugs often are not beneficial in chronic dermatomyositis, but ince occasional success is reported, they should not be w thheld.

M rgan McEll gott treat d 3 patients with the disease fa orabl results were reported in 2

Case 1.—Woman, 30, was acutely ill with dermatomyositis for 2 week Her temperature dropped from 105 F to normal within 12 hours after steroid therapy was started. Rapid improvement continued and treatment as stopped about 3 months after onset. Nine months later the patient was good health with normal musculature.

Case 2.—Woman, 49 had muscle pain and wasting fever cough and purulent sputum. Steroid treatment was started 3 months after onset, and improvement was rapid. Nine months after discontinuing treatment the patient was still symptom free.

Case 3.—Woman, 47 had been bedridden for 6 weeks with generalized muscle pain, tenderness and weakness. She had had an erythematous rash for 4 months. Temporary improvement occurred after steroid therapy but dysphagia and soft-palat paralysi were followed by bronchopneumonia and the patient died. Autopsy howed generalized muscle invol ement.

► [When the diagnosis of dermatomyositis is suspected, all necessary investigative studies should be done promptly including gastrointestinal ay series and genitourinary examination (to rule out possible malignancy) before starting corticosteroid or corticotropin therapy Whereas these drugs would not necessarily confuse the diagnosis of an internal

Bri M J 1311 Dec 29 956

[illegible] they [illegible] the result of some of the other laboratory tests. [illegible]

Clinical and Metabolic Effects of Prednisone, Prednisolone and Cortisone in Patient with Acrodermatitis Continua (Hallopeau) [illegible] reported by Evan Calkins, Leon Reznick and Walter [illegible] (Harvard Med. School)

[illegible]

[illegible] and the nail beds were involved. Patches of similar nature [illegible] on both hypothenar eminences.

[illegible] with prednisone 75 mg. daily and later with cortisone [illegible] mg. daily was not beneficial. Improvement was noticed, however [illegible] treatment with prednisolone 75 mg. daily was started. When the dose was increased to 150 mg. daily the eruption was sup[illegible] [illegible] of therapy however was followed by dissemination of the disease [illegible] maintenance on large doses of prednisone [illegible] months.

[illegible] the disease had been confined to a relatively small [illegible] for almost 40 years, it appears that corticoid therapy and its withdrawal were responsible for the sudden, widespread dissemination. This fact suggests the balance between the disease and the localizing mechanisms must be a tenuous one. This disease appears to be one in which corticoid therapy is not [illegible] in this respect analogous to psoriasis in which [illegible] of therapy with steroids may also be followed by severe exacerbation.

[illegible] patients with rheumatoid arthritis and other debilitating diseases show less than normal tendency to loss of nitrogen, phosphorus and calcium during acute stressful situations or massive [illegible] therapy, a study of the metabolic effects of steroid therapy was carried out in the present patient who had no [illegible] manifestations. Prednisone and prednisolone in [illegible] mg. produced negative nitrogen and phosphorus balances [illegible] cortisone 300 mg. daily [illegible] had little [illegible] nitrogen and phosphorus balance [illegible] in urinary excretion of [illegible]

[illegible] prednisone and prednisolone [illegible] the latter [illegible] the patient [illegible]

continuous prednisone therapy hypertension and congestive heart failure developed.

► [It is not unusual to hear or read of cases in which, although corticosteroids produced benefit or control, severe exacerbations occurred when therapy was ithdra n. In our experience, when this has happened the exacerbation merely appeared to represent the phase the disease would have reached had suppressive therapy not been given. Consideration, however, should be given to the possibility that the balance between the disease and the "localizing mechanisms" must be close indeed. Tipping of this balance ith exacerbation of the dermatosis may occur after administration of really large doses of corticosteroids, such as those given for this patient. —Ed.]

Studies in Local Action of Corticosteroids at Cellular Level in Skin of Man. VIII. Partition Paper Chromatography of Skin Extracts. Leon Goldman, Richard Flatt J S M'hina Jeanette Mier and Emanuel G Daskalakis[3] state that paper chromatography is a valuable aid in the study of the biochemical phase of the action of corticosteroids at the local or cellular level in the skin of man. With su table contr ls, kin biopsies may be submitted for such studies since the specific corticosteroid may be detected even in small quantities.

After hyd ocortison free alcohol injection n the skin paper chromatography rev ealed only free alcohol in the tissue. I jections of the acetate showed in tissue some small quant ties f free alcohol in addition to the larger quantities of the cetate W th 9α-fluorohydrocortisone free alcohol there was a trace of unidentified material running behind the free lcoho l When prednisone free alcohol was injected, usually no material was revealed after 48 hours, whereas after injection f 2 5 mg prednisolone alcohol a small amount was seen. W th local njections of hydrocortisone t-butyl acetate, a mall quantity of hydrocortisone acetate was usually found in the biopsy nd on one occasion there was also an un ident fied steroid less polar than hydrocort sone acetate

R ults with topical pplication of steroid ointment were inconstant Occasionally the steroid was detected in the tissue especially after repeated use Steroids were more commonly found after appl cation of lotions.

In 1 patient, no steroids could be detected in the skin bi opsy 3 hours after oral ngestion of 150 mg cortisone Two patient showed no teroids in the skin 1 hour after intrave nous njection of 33 4 mg prednisolone hemisuccinate. A sk n biopsy taken immediately after the start of a slow drip con

[3] J Invest Dermat 29 1-4, July '57

tumor they might alter the results of some of the other laboratory tests —Eds.]

Clinical and Metabolic Effects of Prednisone, Prednisolone and Cortisone in Patient with Acrodermatitis Continua (Hallopeau) are reported by Evan Calkins Leon Reznick and Walter Bauer[1] (Harvard Med School)

Man 52, had cutaneous lesions on the hands for 39 years. The distal two thirds of all the fingers, except the right little finger were covered on all surfaces with small greenish yellow pustules, superimposed on a sharply demarcated erythematous base All fingernails had been destroyed and the nail beds were involved. Patches of similar nature were present on both hypothenar eminences

Treatment with prednisone 75 mg daily and later with cortisone 300 mg daily was not beneficial. Improvement was noticed, however 4 days after treatment with prednisolone 75 mg daily was started. When the dose was increased to 150 mg daily the eruption was suppressed. Cessation of therapy however was followed by dissemination of the disease, necessitating maintenance on large doses of prednisone over the ensuing 16 months.

Since the disease had been confined to a relatively small area for almost 40 years it appears that corticoid therapy and its withdrawal were responsible for the sudden widespread dissemination This fact suggests the balance between the disease and the localizing mechanisms must be a tenuous one This disease appears to be one in which corticoid therapy is not justified It is in this respect, analogous to psoriasis in which cessation of therapy with steroids may also be followed by severe exacerbation

Because patients with rheumatoid arthritis and other debilitating diseases show less than normal tendency to loss of nitrogen phosphorus and calcium during acute stressful situations or massive corticoid therapy a study of the metabolic effects of steroid therapy was carried out in the present patient who had no constitutional manifestations Prednisone and prednisolone in daily doses of 75 mg produced negative nitrogen and phosphorus balances Cortisone 300 mg daily for 12 days had little effect on the nitrogen and phosphorus balances but was accompanied by increase in urinary excretion of calcium

During the initial metabolic study prednisone and prednisolone produced no sodium retention even when the latter drug was given in a dose of 150 mg daily and the patient was receiving a diet containing 10 Gm sodium chloride Subsequently however over the course of 3 months of nearly

(1) New England J Med 256 345-350 Feb. 7 1957

School and Skin and Cancer Unit) studied 23 patients using the symmetrical paired comparison technic modified to permit evaluation of three preparations (1) 0.5% hydrocortisone free alcohol and 5% coal tar extract in a vanishing cream base, (2) 5% coal tar extract in vanishing cream and (3) 0.5% hydrocortisone in vanishing cream. In all but 1 case marked clinical improvement was observed with the combined hydrocortisone-coal tar ointment at the end of the 1st or 2d week. Comparable results were obtained in 10 patients with hydrocortisone alone and in 1 with coal tar alone. In 9 cases results obtained with hydrocortisone alone were significantly superior to those obtained with tar alone, but in 2 cases the effect of tar was superior to that of hydrocortisone.

In cases in which pruritus was severe, its alleviation was most prompt most marked and most lasting with the combination ointment. No adverse reactions occurred with this preparation Two patients were sensitive to coal tar alone but not to the combination. One patient could not tolerate hydrocortisone when used alone but was not irritated by the combination ointment.

The results obtained with hydrocortisone-coal tar extract cream indicate that these agents have an additive or possibly synergistic effect It appears probable that the favorable effect may result from the anti-inflammatory action of the hydrocortisone acting hand-in-hand with the keratoplastic action of coal tar

► [If one could select but one topical medicament for the treatment of atopic dermatitis it would be hydrocortisone. While very effective when used alone in an appropriate vehicle, its therapeutic value is often enhanced by adding other medicaments which also are of value in this disease, e.g. tar Vioform Diodoquin® and Sterosan® —Eds]

Studies on Local Effect of Various Cortisone Preparations on Experimentally Produced Eczematous Reactions. H Haxthausen[5] (Copenhagen) used electrophoretic patch tests to investigate the inhibitory effect of various preparations on dermatitis produced by introducing a specific allergen into the skin by means of the galvanic current. Immediately after electrophoresis (before the allergic process in the skin had started) the inhibitory test agent was applied.

A weak and inconstant antieczematous effect was noted with hydrocortisone acetate Hydrocortisone alcohol and 9α-chlorohydrocortisone showed a slightly stronger effect

5 Acta dermat venereol 34 33 184, 1954.

taining 25 units of ACTH showed no steroids whereas 2 hours after the beginning of a similar drip biopsy in another patient showed less than 10 µg hydrocortisone

In general although inflammation seemed to cause a somewhat more rapid disappearance of the corticosteroid (demand response of inflammation) the chromatograms were not different from those of normal skin of the same patient

► [*Perhaps further studies of this type will tell us more about the local cutaneous metabolism of corticosteroids used topically in various vehicles.* —Eds.]

Clinical Observations with Nystatin and Fluorohydrocortisone Ointment are reported by Roy L. Kile[3] (Univ of Cincinnati) The preparation used contained nystatin 100 000 units/Gm and fluorohydrocortisone 0 1% in a plasticized hydrocarbon gel base In a series of 106 patients the ointment was most effective in the management of monilial infections occurring in the folds of the body Its most striking effect was observed in certain cases of tinea cruris in which there was considerable irritation. Dramatic results were obtained in 4 cases of otitis externa and in many cases of pruritus ani especially those showing considerable maceration

Many patients who had not done well with nystatin ointment alone showed marked improvement with the ointment which also contained fluorohydrocortisone One patient's skin was irritated by nystatin alone but not by the combination Two patients thought the combination ointment caused increased redness and burning

Epidermophytosis and other types of fungous infections did only fairly well with the nystatin fluorohydrocortisone ointment Probably most of the effect observed was the result of the anti inflammatory action of the steroid present since it has been shown previously that mycotic infections caused by organisms other than Candida albicans do not respond well to nystatin

► [In our hands also the use of combinations containing hydrocortisone or one of its analogues and antimicrobial agents has proved beneficial in the treatment of some *inguinal anogenital and intergluteal eruptions* These combinations have included a steroid with nystatin, with nystatin and Sterosan® with nystatin and Vioform® and with nystatin, neomycin and gramicidin.—Eds.]

Comparative Effects of Hydrocortisone and Hydrocortisone-Coal Tar Extract Creams in Cases of Atopic Dermatitis Sidney G Clyman[4] (New York Univ Post-Grad Med

(3) Ohio M. J. 53 47-48, January 1957
(4) Postgrad. Med. 21 309 313 March, 1957

shown to suppress erythema. Results were about the same with ointments containing 0.5-2.5% hydrocortisone but 0.1% fluorohydrocortison ointment showed a more complete suppression of erythema than 1% hydrocortisone.

The technic used is advantageous because it can be standardized and the skin changes follow a predictable course. Also direct comparison can be made between one part and another of a uniform strip. In a testing of the areas with 2% glycyrrhetinic acid ointments none of the vascular effects of hydrocortisone were produced.

► [If the effectiveness of these compounds to suppress erythema is dependent on their ability to penetrate the skin, it is not surprising that 0.1% fluorohydrocortisone ointment produced more complete suppression of erythema than 1% hydrocortisone ointment. It has been reported on several occasions that fluorohydrocortisone may be absorbed from the skin surface in sufficient amounts to produce systemic effects. The work of Wells provides additional clinical evidence of its superior penetration to the blood vessels of the skin, as compared with hydrocortisone.—Eds.]

Effect of Percutaneous Absorption of Meticortelone[9] on Eosinophil Count was studied by Donald N. Tschan and Leon Adoni (Temple Univ.). Two oz. of 0.5% Meticortelone ointment was rubbed daily into one fourth of the skin surface including affected and nonaffected skin of 20 patients with various dermatoses after the eosinophil count was first determined. A second count was made 4 hours later. In all but 1 patient with an eosinophil count of 100 or more there was a drop in the number of circulating eosinophils. When the ointment base alone was applied to a patient with a count of 224 who had generalized pruritus no change occurred in the eosinophil count.

► [The question of whether the topical application of cortisone and its analogues does produce systemic effects is of continuing theoretical and practical interest. We do not believe that uncontrolled studies such as this will be helpful in elucidating this important question.—Eds.]

Cyclic Estrogenic Hormone Therapy of Acne Vulgaris. Use of Vaginal Smear Technic in Evaluation and Treatment. Douglas Torre and Margaret M. Klumpp[1] (Cornell Univ.) treated 21 female patients, aged 13-20, with acne vulgaris. The patients also had evidence of ovarian insufficiency; 9 had menstrual irregularity and 8 had dysmenorrhea. A preparation of conjugated estrogenic substances was administered orally for 14 days before the expected date of the menses. Usual starting dose was 1.25 mg. daily. With each succeeding cycle the dose was raised 1.25 mg. daily until a

(9) J. Invest. Dermat. 27:[illegible] 1956, June, 1957.
(1) J.A.M.A. 164:[illegible] July 27, 1957.

while results with substance 166" (a Xantogen derivative) and 9α fluorohydrocortisone were still better Further investigation of the fluor derivative of hydrocortisone indicated that this substance is almost as effective in a 0 1% concentration as in 2 5% strength Since serious reactions have been reported when large amounts of the more concentrated ointment are applied to the skin use of the 0 1% concentration offers a means of achieving good therapeutic results with minimal risk. Unfortunately the antieczematous action of the fluor derivative of hydrocortisone is not entirely constant. In some cases it wholly or almost wholly suppresses the reaction while in others it has no effect. Because of this Haxthausen suggests that the therapeutic effect of the preparation in the individual case might be investigated by means of the electrophoretic test before treatment is started The test is easy to perform and results can be evaluated in 24-48 hours

► [In practice it has been our experience that when one topical corticosteroid fails another may do the job satisfactorily This occurrence is rare however providing the chosen corticosteroid is dispensed in the proper concentration and appropriate vehicle in the first place.—Eds.]

Effect of Hydrocortisone on Standardized Skin Surface Trauma is reported by G C Wells[6] (Univ of London) The effect of cortisone derivatives as observed under the capillary microscope is to inhibit vasodilation. If an irritant is subsequently applied to both hydrocortisone treated and control areas of skin there is greater reaction in the former associated with burning pain suggesting the treated area was held in a state of greater susceptibility to the effects of the surface irritant than the control Histologically a heavier perivascular lymphocytic infiltrate is noted in the upper dermis of the control areas

In a study of the local action of hydrocortisone most of the keratin was removed from the skin by repeated stripping with cellophane tape, leaving after about 30 pulls a transparent denuded surface with persistent erythema At 4-6 hours after application of hydrocortisone the treated strip was paler than the control at 12 hours the difference was maximum the hydrocortisone treated area often being a pale as the normal skin by 24 hours the difference was le as the control faded and by 48 hours it was much les

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(6) Brit. J Dermat. 69 11 18, January 1957

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[3] [illegible] Dermat. 28 [illegible] June, [illegible]
[4] J A M A. 144 1447 [illegible] July 27 [illegible]

good clinical result was obtained or the vaginal smear showed adequate physiologic response as indicated by normal cornification. Dosage was then decreased by 1.25 mg daily in succeeding cycles as long as improvement held. Average length of treatment was 8.9 months and average daily dose was 3.9 mg. Results were good in 7 patients, satisfactory in 9.

In a second unselected group of female patients with acne vulgaris aged 11-30, 8 received only a placebo, 12 received only estrogens, 16 received a placebo followed by estrogens and 14 received estrogens followed by a placebo. Courses of hormonal and placebo therapy were alternated without knowledge of the patient. Results of estrogen therapy were good in 24 of 42 patients (75-100% improvement) and satisfactory in 13 (50-75% improvement). Length of treatment averaged 6.8 months; maximum daily dose averaged 6 mg. No good results were observed in the 8 patients receiving only placebo or the 16 who received placebo before estrogens; satisfactory results were seen in 2 patients.

In correlating maximum estrogen dosage with findings on vaginal smear in successfully treated patients, it was found that those patients with evidence of estrogenic hormone deficiency required on the average higher doses than those with apparently normal ovarian function. The results indicate that administration of estrogens in the postovulatory phase of the menstrual cycle is of value in treatment of acne.

The following conditions were considered contraindications to estrogen therapy: (1) endometriosis, (2) evidence of persistent ovarian follicle, (3) cystic mastitis, (4) carcinoma of breast or female reproductive organs, (5) ovarian cyst, and (6) severe liver disease.

► [As do the authors, we too feel that the postovulatory administration of estrogenic hormones in selected patients with premenstrual acne flareups is often of distinct value. The selection of patients is important and should include the following: (1) history of definite and regular premenstrual acne exacerbations, (2) no history or evidence of the contraindications listed by Torre and Klump. In addition it would be wise to question concerning family history of carcinoma of the breast or genital organs. While there is no distinct proof of the carcinogenic effects of therapeutically administered estrogens in human females, one would hesitate to prescribe them when there is a family history of such cancers. (3) opportunity to see the patient at regular intervals, (4) failure to respond satisfactorily to other forms of therapy.

In our own experience a dose as little as 0.625 mg Premarin® given daily beginning 10 days before the expected onset of menses, is sometimes sufficient. Our usual starting dose is either 0.625 mg or 1.25 mg and only

rarely do w exceed 2.5 mg. per dose. Beginning treatment 10 days before onset of the menstrual period can usually be depended on to allow for ovulation starting treatment earlier than this during the cycle may interfere ith ovulation. If estrogen therapy fails to help after several months trial it should be discontinued. If effective, an attempt can be made from time to time to discontinue the medicament so that it is not used longer than necessary Of course if dysmenorrhea, amenorrhea, metrorrhagia, etc occur estrogen therapy should be stopped. It should be mentioned, how ever that on occasion some of these very difficulties are benefited by estrogens. Eds.]

B PHYSICAL THERAPY

Dermatologic Radiation Therapy in This Nuclear Age—Appraisal is presented by Paul M. Crossland* (Stanford Uni) Recently physicists and radiation health officers have been sounding alarms regard ng the perils to mankind of a slowly increasing burden of radiation exposure. Unfortunately the public is beginning to mistrust radiation exposure to the point where many patients are refusing necessary di agnostic and therapeutic procedures. Even in the medical journals statements have implied that the nonradiologist may be adding unjustifiably to man s mounting lifetime exposure by careless and unwarranted use of radiation. The seeds of doubt and mistrust have thus been planted in the minds of many physicians. It i time to separate facts from fancies among these fears.

In dermatology the need for radiation therapy has been greatly reduced by recent developments in pharmacology and endocrinology Striking successes with the use of antibiotics and steroids hav led to abandonment of radiother apy in many diseases In others, its use has been rendered more precise by new advancements in radiology There is an mportant trend toward use of softer radiation whenever uch ray are effective. In the future radioactive isotopes will no doubt be used instead of radium and radon whenever the former w ll gi e equal or better results with less danger t operator and patient. The purpose of their use in derma tologi therapy will be not only to lim t the depth dose but als t tta n greater specificity n irradiation than is possible w th other radiati e means.

The dermatologist of today is roentgen conscious and bent on u ing radiation spari gly as he would any powerful medi cine H realizes that ionizing radiations are destructive

* J.A.M.A. 165 647-650 Oct. 12, 1957

rather than stimulating However they are still the most effective agents for the treatment of certain diseases including some that are benign but nonetheless disabling To answer the question whether unnecessary harm is being done by use of ionizing radiations, it is necessary to consider how the dermatologist uses radiation therapy

First he uses localized radiation therapy Localized body exposure has only the fractional significance of total body exposure Localized irradiation even with large doses produces no serious systemic effect thousands of people who have been so treated for skin cancer have remained healthy Second, the dermatologist uses superficial radiations with half value layers of 0 02 3.5 mm Al For treatment of benign dermatoses the half value layer is usually less than 1 mm Al Radiations of this quality applied to the skin are insufficient to damage the liver spleen bone marrow or reproductive organs Third dermatologic radiation doses are small comparatively speaking and are usually fractionated. As soon as the disease begins to respond treatments are discontinued or spaced farther apart because the effect of ionization continues for some time In this way the lowest possible dose is given

Superficial therapy of benign diseases has been criticized because of the possibility of serious sequelae However in a study done at the New York Skin and Cancer Unit no sequelae had resulted from total doses of 1 000 r when 1 000 patients were re-examined 5 23 years after treatment It is true that the use of radiation for treatment of benign diseases should be justified in every case The dermatologist is not primarily concerned with radiation but with cure of skin diseases His ability to diagnose skin diseases correctly and his knowledge of the various therapeutic approaches enable him to save his patient from unnecessary irradiation Not many unnecessary roentgens are being added to man's increasing systemic radiation burden by the qualified dermatologist

Everyone receives about 15 r total body irradiation from cosmic rays during his lifetime The Atomic Energy Commission has estimated that the amount each person has received from all nuclear detonations to date (0 1 r) is less than 1/100 of the average total lifetime dose from cosmic rays Although the long range effects of radiation are unknown perhaps there is no reason to assume that all these effects

w ll be bad and that there are no hidden remedial factors Experiments ha e hown that the life span of mice and rats hortened by total body exposure to radiation above a cer tain limit of tolerance Yet the span of human l fe has in creased by 20 years since the discovery of ionizing radia tions A hare of this increase is certa nly due to accurate and prompt diagnoses made possible by use of diagnostic x-rays, and therapeutic use of x rays has also lengthened the lives of ma y patients.

Within the med cal profession the fear of radiation therapy ha been heightened by the fact that one medical group has pointed n ccusing finger at other groups for misusing it. Actually a few in all these groups have misused this modal ty Th criterion for u ng ionizing radiation should be that the user trained n and understand radiation physics and biophy cs and that he knows what he is treating rather tha that he hould be a member of any particular coterie \ ca d dat can be cert fied by the American Board of D rmat logy unles h is adequately tra ned n radiation and b phy ic pertaining to uperficial therapy and knows the d at nd contraindicat n for irradiation of skin l seases

► [Because of the increasing resistance on the part of some physicians and the public to the use of radiation therapy feel that every physician should know the facts (and the truth) about this modality and every dermatologist should be ell prepared to counter the arguments of the antagonist t of this form of treatment W are in complete accord with the attitude taken by Crossland and w also champion the selected use of ionizing radiation in dermatologic practice

Recently the junior editor th Sulzberger and Stewart, reported on series of studies designed to find the possible sources of radiation reaching the gonads of patient during radiation therapy of arious diseases of the skin and to devise method to educe or eliminate any radiation which might reach the reproductiv organs (See following article)—Eds]

Studies on Quantity of Radiation Reaching Gonadal Areas during Dermatologic X Ray Therapy I. Preliminary Report. Victor H Witten, Marion B Sulzberger and William D Stewart (New York Un Post-Grad. Med School and Sk n and Cancer Unit) mea ured the radiation reaching the gonadal a ea of males and females during routine x-ray therapy f arion dermat logic condition

Of the 38 readings recorded on 16 pat ents 20 were on 8 patient treated in a horizontal position. The kin condit n treated were ene vulgari in 6, foot eczema in 1 nd

1 J Invest. Dermat 24 57 195 February 17

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will be bad and that there are no hidden remedial factor Experiments have shown that the life span of mice and rats shortened by total body exposure to radiation above a certain limit of tolerance Yet the span of human life has increased by 20 years since the discovery of ionizing radiation A share of this increase is certainly due to accurate and prompt diagnoses made possible by use of diagnostic x rays and therapeutic use of x-rays has also lengthened the li of many patients

Within the medical profession, the fear of radiation therapy has been heightened by the fact that one medical group has pointed an accusing finger at other groups for misusing it. Actually a few in all these groups have misused this modality The criterion for using ionizing radiation should be that the user is trained in and understands radiation physics and biophysics and that he knows what he is treating, rather than that he should be a member of any particular cater No candidate can be certified by the American Board of Dermatology unless he is adequately trained in radiation and biophysics pertaining to superficial therapy and knows the indications and contraindications for irradiation of skin diseases

► (Because of the increasing resistance on the part of some physicians and the public to the use of radiation therapy feel that every physician should know the facts (and the truth) about the lity and every dermatologist should be well prepared to counter the arguments of the antagonists of this form of treatment We are in complete accord with the attitude taken by Crossland and also champion the selected use of ionizing radiation in dermatologic practice

Recently the junior editor with Sulzberger and Stewart, reported on series of studies designed to find the possible sources of radiation reaching the gonads of patients during radiation therapy of various diseases of the skin and to devise methods to reduce or eliminate any radiation which might reach the reproductive organs (See following article)—Eds]

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rather than stimulating However they are still the most effective agents for the *treatment of certain diseases including* some that are benign but nonetheless disabling To answer the question whether unnecessary harm is being done by use of ionizing radiations it is necessary to consider how the dermatologist uses radiation therapy

First he uses localized radiation therapy Localized body exposure has only the fractional significance of total body exposure Localized irradiation even with large doses produces no serious systemic effect thousands of people who have been so treated for skin cancer have remained healthy Second the dermatologist uses superficial radiations with half value layers of 0 02 3 5 mm Al For treatment of benign dermatoses the half value layer is usually less than 1 mm Al. *Radiations of this quality applied to the skin are insufficient* to damage the liver spleen bone marrow or reproductive organs Third, dermatologic radiation doses are small comparatively *speaking* and are usually *fractionated*. As soon as the disease begins to respond treatments are discontinued or spaced farther apart because the effect of ionization continues for some time In this way the lowest possible dose is given

Superficial therapy of benign diseases has been criticized because of the possibility of serious sequelae However in a study done at the New York Skin and Cancer Unit no sequelae had resulted from total doses of 1 000 r when 1 000 patients were re-examined 5-23 years after treatment It is true that the use *of radiation for treatment of benign diseases* should be justified in every case The dermatologist is not primarily concerned with radiation but with cure of skin diseases His ability to diagnose skin disease correctly and his knowledge of the various therapeutic approaches enable him to save his patient from unnecessary irradiation Not many unnecessary roentgens are being added to man's increasing systemic radiation burden by the qualified dermatologist

Everyone receives about 15 r total body irradiation from cosmic rays during his lifetime The Atomic Energy Commission has estimated *that the amount each person has re*ceived from all nuclear detonations to date (0 1 r) is less than 1/100 of the average total lifetime dose from cosmic rays Although the *long* range effects of radiation are unknown perhaps there is no reason to assume that all these effects

n practice, such as voltage voltage form filter diameter of th field, focus-skin distance composition of tissue and thickness f the layer to be irradiated, then with the help of su h a measuring procedure graphs and depth-dose curves could be composed that might serve as a valuabl aid in therapy

To obtain the desired data experimentally the theoret ically and experimentally verified law of Bragg-Gray is used. This law states that the ionization current in a mall ai filled cavity in tissue is a measure for the ionization den sity in that tissue at the place of th s air cavity Phantom ma terial that for a great range of wave lengths has approxi mat ly the same absorption coefficient as soft ti sue i used. Withi such a phantom an ionization chamber is placed the chamber is filled with air and the ionization current occur ring f x rays are thrown on the phantom is measured with a electrometer

In this way investigato s have composed depth-dose curves and isodose curves The grenz rays and the more pen trating radiation aroused particular nterest the range between 50 and 100 kv with filter however was not stud ed in the past and thus the range used most often by the majority of der matologists. For thi reason J J Zoon and J F C Werz[3] (Un v of Utrecht) took measurements in th s range using as a phantom perspex a material corresponding to sk n in atomi composition. In order to have available the data re qu red for the more uperficial skin diseases, the depth of demonstrable alterations in a large number of skin biopsies was measured. From these measurements a subdivision nto three groups was made (1) Disorders with alterations down to 1 mm many eczemas, many cases of psoriasis, nevus flammeus (2) Disorders down to 2.5-3.5 mm. chronic li-chenified eczemas circumscript neurodermatitis lichen planus, lichen ruber corneus, psoriasis infiltrati e changes in granuloma fungoides types of acne and many others (3) Disorders with changes deeper than 3 5 mm skin tumors deeper inflammations hidradenitis, mycosis tumors and other reticuloses and many others.

For its nutrition and regeneration the epidermis depends on its subjacent layers. Therefor it appears likely that r radiation of the cutis, nd poss bly the subcutis actually may

(3) A.M.A. Arch. Dermat. 75 [illegible], Ma 957

hydradenitis of the thighs in 1 Doses to the gonadal areas from stray and scatter radiation in this group were 2 125 mr/treatment when 85-340 r were delivered When 3 treatments were given at 1 sitting (1 to the face 1 to the back and 1 to the chest representing 510 r total) 140 mr were recorded at the gonadal area

Each of 2 patients in the supine position received 2 treatments with filtered radiation having half value layer of 2.1 mm Al The condition treated was hidradenitis suppurativa of the axillae in 1 patient and of the thighs in the other Both treatments to the thighs (170 r each) and 1 to the axillae (340 r) delivered a dose of more than 200 mr to the gonadal areas When the axillae were irradiated at a subsequent sitting (total 340 r) the dose to the gonadal area was in the range of 125 mr These patients were carefully shielded and placed in position

In the last group there were 14 readings on 6 patients in the sitting position with hands or forearms being treated for psoriasis, nail changes and verrucae In 3 patients cones were used to limit the irradiated field in the others, lead shielding was placed around the irradiated field. In those receiving 85-170 r irradiated without cones but with conventional shielding the dose to the gonadal area was 50-158 mr In those receiving 85-510 r treated with cones the dose was 3-196 mr

It is suggested that the distance from the x ray tube to the gonadal area should be increased to the maximum consistent with good therapeutic technic by proper placing of the patient and other means Shielding of the gonadal area should be done routinely in x ray therapy

► [Additional studies on this subject by the same authors have resulted in (1) technics which utilize shielding materials which are readily available, inexpensive and easily handled, (2) procedures which are simple and speedy and cause no discomfort or undue alarm to the patient, and (3) considerable reduction in the gonad dose to such a level that the concern which has been voiced concerning the possible genetic effects of therapeutic radiation as given for most dermatologic disorders may be greatly alleviated.—*Eds.*]

Quality of X rays in Treatment of Skin Diseases. According to present concepts the effect of x irradiation is based on the ionizing potency of rapid electrons arising from absorption of roentgen quanta. If a method of measuring were available, in order to determine the *ionization density in tissue* as a function of various parameters that are important

of face 10-15 r da ly or 20 r of medium x rays 3 times a week was gi en until marked in olution of acute inflammat ory in filtration was noted (i e after an a erage c f 6-10 se ion) Pat dim n shed mostly after a few se m Sim larly acute oozing eczema particularly those which pr ed refractor t topical treatment (e g eczema cruri) and e en painful ecz ma f the leg were irradiated daily with 10-15 r r 3 t mes a week with 20 r of soft radiation of 30 kv with 0.5 mm Al filter Exudation mostl eased after 8-1 e n an l local therapy could be in t tuted again In a t tal of 59 pa t ent w th diseases thu treated only (failure occurred Th t pe of rradiation therapy i ad a tageou in that ef fect ar hieved with strikingly mall total l ses

[W ta ery effective method of radiation therapy which utilizes ra of softer quality and deli ers fewer oentgens I priv te practic it is often difficult, however for the patient to return fo treatment daily even 3 times eekly

It ould hav been desirable to ha different lesions in the same patient treated simultaneously ith small dose -ray herapy 3-5 times eekly and ith 75 once weekly I the discussion, W Pierekha It stated that he had irradiated symmetrically situated eczema area imultaneously with different doses H found 20 or 40 more effectiv than 80 but did no giv the time intervals at hich the different dosages ere administered —Ed]

Mechanism of Action of Teleroentgentherapy I Its Possibilities in Dermatology Ant onio Chia enza (Un f Catania) used t leroentgentherapy on 87 pat ent w th ariou dermatoses Factors wer 15 r/field focus-sk n di ta ce 150 cm 150 kv 8 ma ml mm Al filter for a t t l dose f 45-60 r fi ld Th dose wa del vered w th the Vigliardo Gorla Siama apparatu to the posterior and anterior urface of the body alternately on alternate day r to the posterior half of the body consecut ly on lternate day or to the 4 sections of the anterior and posterior urface within 24 hours. Testes and o aries were protected with lead plates a wer kin lesions n some patient with localized eczema so as to l m nate the direct action of th x-ray on the kin

Result were good in local zed nd diffuse eczema and excellent in Darier disease (with reco ery) i f ll culit of the lower extrem tie and in pityria i rosea Pruritu decreased, eruption became rreated and papular element regressed or disappeared in patients with lichen plan Im provement was transitory n chronic lupus erythematosu and in exfoliative erythroderma of Wilson Brocq type The

( ) Minerva dermat 3 344 351, November 1956.

influence the epidermis For the greater part of the body surface it is established that below the skin are situated tissues that are only slightly radiosensitive It therefore appears justified in the absence of radiosensitive tissues such as the eye or testis not to be too cautious with underlying tissues, and to try to obtain a homogeneous irradiation of the diseased and altered portion of the skin Therefore preference will be given to irradiation that has been deprived by a filter of the softest components because these reach only the most superficial layers Recognition of the fact that none of the dermatoses shows a constant thickness of the affected layer and that the thickness cannot be determined with complete accuracy must lead to the conclusion that use of unfiltered irradiation results in a very irregular distribution of radiation energy over the pathologic tissue

From this consideration and on the basis of data from the literature and their own measurements the author suggests the following irradiation formula (1) For the most superficial dermatoses 25 kv with a half value layer of 0 1 mm. Al (2) For alteration 1 3 mm deep 85 kv with 0 5 mm Al HVL (3) For disorder deeper than 3 mm 70-100 kv a c with 1 3 mm Al HVL

► [It is only logical to apply a therapeutic modality directly to the diseased tissue, if at all possible This holds true for ionizing radiation as well as topical medicaments. It makes sense, then, to select the quality of radiation that delivers the greater share of its energy and thus produces its major biologic effect, in that part of the tissue which is most involved That is why in our opinion there is a definite place in dermatologic therapy for grenz radiation, low voltage and conventional x-radiation, as well as thorium X cathode rays and radium.—Eds]

Experiences with Small Dose Roentgen Therapy in Acute Inflammatory Processes are reported by Emil Fischer[3] (Univ of Zurich) For some time acute inflammatory processes e g furuncles paronychia hidroadenitis have been treated successfully with x rays the therapeutic effect of which was believed to be due to disintegration of leuko- and lymphocytes with subsequent liberation of antibodies and institution of fermentative actions inflammatory acidosis turns into long lasting tissue alkalosis Whereas previously comparatively large single doses of 80-150 r had been applied amazingly good results with small-dose therapy (10-20 r) have been reported lately To furuncles paronychia hidroadenitis deep trichophytosis of scalp and bearded area

(3) Dermatologica 114:204-208, 1957

injectable material was used on each occa ion to distend and blan h each keloid complet ly In half the cases injections were gi en twice weekly and in the other half at 7 10 day i tervals for an average of 10-12 injections. (4) A series of intralesional injections of hydrocortisone and hyaluronida e followed by surgical removal of the keloid immediately after the last injection. An ointment containing hydrocortisone neomycin and hyaluronidase wa applied twice daily to the healing wound (16 lesions) (5) A series of intralesional injections of hydrocortisone and hyaluronida e followed by radiotherapy (16 lesions) (6) A series of intralesional injections of hydrocortisone and hyaluron da e followed by surgery and rad otherapy Simple excision and suture or shaving of the lesion flush with the kin urface followed by application of a cautery just sufficient to stop bleed ng were the urgical method used. The latter method appeared to produ e the better cosmet c result (30 lesions)

The percentage of mprovement or permanent cure was not ceably higher w th the la t routine making it the present m thod of choice Recurrences u ually started within 3 months of completion f treatment and none was noted after 6 months All failures nd nearly all recurrences involved k loids of 2 or more years duration in which no pink coloration was present. Itching and tenderness, when present, were more qu ckly relieved by intralesional injections than by radiotherapy Combined njections of hydrocortisone and hy l ron dase caused less local discomfort than injections of hyaluron dase alone, and the combination appeared to gi e better results than e ther substance alone. In cases with disappearance f the keloids but unsat factory cosmet c result whitish, wrinkled, atrophic skin usually remained which was soft to the touch owing to lack of fibrous content

► [Actually the method which combined the three pproaches used by Belisario (hydrocortisone-hyaluronidase injections plus surgery plus radiation) produced the best results Unfortunately there still is no ay to remov satisfactorily all keloids without recurrence, since even the best method leaves much to be desired. Though undoubtedly known to all, it is worth repeating that solid carbon dioxide is worth a trial, particularly in small keloids. W hav also seen flattening and softening of keloidal scars after thorough X therapy.—Eds]

X-ray Treatment of Keloids is discussed by F F scher and H Storck[4] (Univ of Zurich) who report a 20-year period f llow-up study conducted on 316 patients. The thera

[4] Schweiz med Wchnschr 87 128 283, October 1957

treatment had no effect on microbial eczema chronic pruritus psoriasis (the latter showed a greater tendency to spread) Duhring's disease, bullous pemphigus pseudokeloid hypertrophic folliculitis trophic ulcer and condyloma acuminatum It had almost no effect on spinocellular epithelioma and tuberous serpiginous syphilis Controls before and after therapy revealed no marked changes in glycemia azotemia, blood pressure testes and ovaries sedimentation rate and hepatic and renal function Decrease in white blood cells after the first irradiations sometimes occurred to the point of true agranulocytosis but did not necessitate discontinuance of therapy changes in the red blood cells were mild and in some instances the number of eosinophils increased slightly *The therapy was well tolerated but it could not prevent* relapse

As to its mode of action in dermatology teleroentgentherapy may affect the skin by stimulating radiosensitive organs and tissues With its destructive effect on leukocytes (agranulocytosis) it may liberate proteins capable of producing bacteriolytic and antitoxic antibodies It may stimulate the reticuloendothelial system and thus increase the production of circulating antibodies. Or it may exert a general action on the organism as a whole and thus create in the milieu a change capable of preventing the development of or even of destroying pathologic tissues

► [The trend in dermatologic radiation therapy should be toward x radiation of softer quality so that the effective portion of the radiation spectrum is absorbed in the diseased tissue rather than reaching the blood vascular system, hemopoietic tissues and other deep organs. Why use such hard radiation for widespread superficial dermatoses? Technics such as that used by Schirren (J Invest. Dermat. 24 463 1955) by which the radiation is delivered at 2 m. distance, 50 kv 25 ma. through a beryllium windowed tube, appear *much more suitabl for the management of diseases* f the skin with teleroentgentherapy.—Eds.]

Treatment of Keloids. John C Belisario[5] (Sydney Australia) compares results obtained in the treatment of 114 keloids by 6 different routines (1) X ray treatment in doses of 400 r monthly for 3 doses 200 r every 2 weeks up to 6 doses, or 150 r weekly up to 8 doses (10 lesions) (2) Scalpel or electrosurgery followed by radiotherapy (12 lesions) (3) Intralesional injections of hydrocortisone acetate 25 mg/ml. hyaluronidase 150 Wydase units/ml or a combination of the two (10 lesions by each routine) Sufficient

(5) Acta dermat.-venereol. 37 165-181 1957

bl to irradiation All 15 had 4 r more x ray treatments or series of treatments

Surgical instead of x ray treatment i nggested for keloid extending over joint x-ray onl soften these and l m t improve the functional insufficiency cau ed by the scar tis ue Vaccination keloid often resi t x rays and therefore call for surgical repair Radium appears to be a efficient a x-ray irradiation in treatment of keloid but wa given up b the author because of ts deep effect and the difficulty f handling it

► [Additional studies of this type should be undertaken by other groups ho hav access to large patient material The information gained from such studies is of great value —Eds.]

Influence of Irradiation of Pituitary Gland on Acne. Thomas Butterworth and George W Chamberl n[1] (Reading Pa) pplied x-ray therapy to the pituitary glands of 53 patients with acne without adjunctive therapy In the first group of cases 33 were administered to the pi u tary da ly for 4 days 23 patient and daily for 6 days in 2 patient Facto used were half value layer 0 95 Cu 200 kv 15 ma. 54 cm fi ld size 6 cm diameter The dose wa 100 r a mea ured in ai to alternating lateral temporal field The second gr up con isted of 28 patient who received 33 r t their pituitaries weekly for 8 weeks. Factor used were half-value la er 1 04 Cu 200 k 15 ma., 50 cm field ize 6×8 cm

About two th rds of the patients in each group howed great improvement or were entirely cured About 10% of patients fa led to respond to t eatment. Striking response w noted n a girl, age 20 who 1 year previou ly had rece ed the lim t of perficial x ray administered to the sides f the face In th fir t group mprovement u ually occurred w thi 2 month of treatment and often a quickly as 2 or 3 week after therapy Results occurred more slowly in the second group u ually appearing 2-4 month after the last treatment Follow up of 23 of the 25 patient in the first group 16-18 months after rradiation howed greater improvement 7 patients and somewhat less mprovement in 3 Two pa t ents who had recei ed 6 daily treatment and 5 who had had 4 daily treatments experien ed moderate hair loss o er the temporal treatment fields. In every nstance regrowth wa complete

A psychic effect must not be overlooked as a pos ible influ

(1) A.M.A. Arch. Dermat. 75:502-506. April, 1957

peutic effect was termed "good" if the keloid softened and its surface levelled off "fair" if the softening was only moderate and the keloid was still somewhat elevated from the skin surface "unaffected" *if the keloid remained unchanged or became even coarser than before* Most patients were followed for at least 5 years

It was found that good results were achieved in 83.3% of keloids resulting from injuries surgical scars or infections and in 58.3% of keloids developing after burns scalds or caustic injuries The number of "unaffected" patients was 4% the same in the two groups It was also observed that small punctate or linear keloids regressed much better after x ray treatment than keloids extending over a large area such as those seen after burns or scalds Results were better the *sooner x ray treatment was started Keloids responded to* x ray treatment best within the first 6 months after their appearance good results being obtained in 75% of the patients On the other hand, there was no significant difference in therapeutic results whether irradiation was given during the first 3 months or during the 4th to 6th months

Among 21 patients who received prophylactic x ray treatment after healing of their surgical wounds keloid development could be suppressed in only 12. Therefore the author do not encourage irradiation for prevention of keloid formation

Single doses of 400 r at interval of 4-8 weeks (1 000 r with grenz rays) were used or for large keloid 200 r in each of 3 weekly treatments Total dose amounted to 800-1 600 r in the former and to 1,200-2 400 r in the latter treatment ched ul Only on rare occa ions was a higher dosage delivered The treatment period lasted 2 5 months.

Regression of the keloid was detectable at the end of x ray treatment in 65% of pa ient Speed of regre ion seemed to be independent of the quality of x ray used The efficiency of x rays in treatment of keloids cannot be judged by regre sion alone one has to consider also the late cosmetic effects of irradiation such as atrophy pigment changes and telangiectasias However since these late effects may appear even without x ray treatment especially after burns a final evaluation is rather difficult After a 5-10 year follow up only 15 of 292 patients (5 13%) demonstrated *late change attributa*

period n ? 1 of the latter proved to be a case of pemj h gu

Effects of para ertebral irradiation in 63 pat ents with ari ous types of pemphigus were less sati factory although not inferior to results achieved with other drug Favorabl ef fects included faster epithelization and diminution in the n mber of fresh bullae a few patient finally became a ymptomatic and in 5 the condition previously serious and gen eralized became localized, with recurrences appearing only within circumscribed area Localized pemphigus showed complete in olution after irradiation of the correspon l ng segment Exacerbation were seen to occur 4-8 da after irradiation and were segmental even in generalized pem phigus i localized types they appeared within the previ u ly nvol ed area and after irradiation of the re pective segment Generally exacerbations disappeared within 6-10 days, and in only 4 ca es were they followed by last ng deterioration Despite the poss bil ty of such effects para ertebral rradiation is not risky and often beneficial when other drugs are contraindicated or have been used without success.

The mechanism f the effect of paravertebral irradiation may be explained by ts action on inflammatory changes in spinal ganglions f pemphigus pat ents. When regressive degenerati changes preva l, no ffect can be expected. An indirect act on on the vegetative-hormonal system cannot be excluded.

Lichen Planus Treated with Grenz Rays Preliminary Report is presented by H Kopp and Fritz E. Reymann (Copenhagen) Twenty patients with extensi e symmetrical eruption of lichen planus were gi en 3 treatments of 200 r ea h at weekly intervals Only the right side of each pat ent wa t eated with grenz rays a simulated treatment without actual administration f grenz ray was given to the left side Three week after treatment was started the lesions on the right side were considerably les severe than those on the left Three treatments of 200 each were then given at weekly tervals to the left side of ea h patient At the end of 6 weeks, improvement was about equal on both sides in most patients At this time 12 patients were complet ly clear 4 were greatly improved and 4 showed little improvement

► [In our experience, grenz rays are of benefit in the management of lichen planus. Does of 200 given eekly for 4 or 5 treatments will aid

(9) Acta dermat.-venereol. 34 477 481 1954

ence in the results obtained Many of the patients however had had previous ultraviolet light local remedies and additional measures without benefit In addition 7 feebleminded patients, in whom a psychic factor might be less important showed the same improvement as the others.

The effect of small doses of roentgen or gamma radiation on the function of the hypophysis is unknown. Perhaps the pituitary sebaceous gland tropic factor is depressed Or results might be due to irradiation of the hypothalamus, thus indirectly affecting the hypophysis These results are presented only as a possible stepping stone toward the ultimate understanding of the pathogenesis of acne. In no sense is irradiation of the pituitary advocated as a routine measure in treatment of acne.

► [The results of this study could be much better evaluated if there were a control group of patients who were treated during the same season of the year and exactly the same in every way including being prepared for x radiation under the machine, but without turning on the high voltage. We feel that such control cases are necessary especially because many experts are of the opinion that the cells of the pituitary are radioresistant. —Eds.]

Indirect Vertebral X ray Irradiation in Dermatitis Herpetiformis and Pemphigus was used by Nikolaus Thoroczkay[8] (Univ of Budapest)

METHOD.—Corresponding to the age of patients and the seriousness of existing symptoms 50, 100, 150 or 200 r (160 kv 0.5 mm. Cu. +1 mm. Al filter) were applied 2 3 (occasionally 5 7) times to 4 areas of the vertebral column at intervals of 8 10 or 14 days. In localized types the corresponding segment of the spinal cord and when the oral cavity was involved the region of gasserian ganglions was irradiated. Ointments were applied topically and vitamins C and B and occasionally other drugs, were given.

Of 37 patients with dermatitis herpetiformis 28 responded amazingly well to paravertebral irradiation Formation of bullae ceased and pruritus lessened 4-8 days after termination of treatment, and after 2-4 weeks patients were free from symptoms or at least from complaints and remained so for months even years Only in 9 cases did paravertebral irradiation have to be prolonged or combined with Spirocid Plasmochin® Aureomycin® ACTH cortisone local x ray or grenz ray irradiation Unfavorable reactions mostly consisted of slightly increased itching which was generalized in 8 and limited to irradiated segments in 10 patients Recurrences were seen after 6 months in 9 cases and after a longer

(8) Hautarzt 8:267-270, June 1957

tion reaction results were much less satisfactory because adequate doses could not be given

[We do not favor use of any form of ionizing radiation for treatment of benign lesion of only cosmetic importance If there is high incidence of tissue destruction and alteration resulting from the method. I grenz ray (Bucky ray) therapy of nevus flammeus such massive doses of radiation must be given that there is definite chance of producing atrophy, telangiectasia and pigmentation. Therefore, cannot accept the method as being entirely safe or desirable On the other hand, thorium X, conventionally used for treatment of nevus flammeus, can be employed without fear of atrophy or telangiectasia.—Eds]

Experiences with Ultrasonics in Dermatology Ultrasonic waves are mechanical oscillation of high frequency those between 75 and 3000 kc are used for therapeutic purposes These mechanical oscillations are said to produce in tissue tension and pressure effect which cause a kind of cellular micromassage with various biologic effects (e g shifting of ions and water changes of tissue pH permeability of cellular membranes respiration metabolism and resorption in tissues increased blood and lymph circulation generation of friction and adsorption heat) Various vasomotor reactions are also produced in the skin.

In over 3,000 sessions, Friedrich Maag[2] (Univ of Zurich) using two sets of vibrators treated 180 patients most of whom had ulcus cruris traumatic ulcer roentgen ulcer or acne vulgaris Between 1 and 2 watts/sq cm. was used with one set and 0 1 1 watt/sq cm. with the newer set

Traumatic ulcus cruris responded better to ultrasonic treatment than did postthrombotic and constitutional varicose ulcers Side effects included twitching painful sensation (obstructed arterioles) increased dermatitis around ulceration and deep periosteal pain Of 26 irradiation (x-ray radium) ulcers 8 were definitely cured Among 5 patients with acne vulgaris which had been unsuccessfully treated by x ray ultra violet light, antibiotics, vaccines vitamin hormones and sulphur preparation ultrasonic therapy was followed by improvement in 40% and by complete cure in 12% Duration of ultrasonic treatment was long sometimes over 13 months One patient had side effects consisting of nausea and dizziness. In eczemas psoriasis, Dupuytren contracture, induratio penis plastica, scleroderma and sclerodactylia, results were negative

Focused ultrasonic treatment (caustic ultrasonic therapy)

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(2) Dermatologica 115:121 33 August, 1957

in the resolution of lesions in some cases. However, grenz rays should not be depended on as the sole therapeutic approach.—Eds.]

Radiation Therapy of Nevus Flammeus with Bucky Rays was used by Jaroslava Maresova[1] (Univ of Prague) in 91 patients since 1949 Deep red or bluish lesions were present in 11 patients and light red superficial nevi in the others. The lesions were present since birth and no tendency to spontaneous disappearance was observed. The following technic was used half value layer 0 02 mm Al 12 kv and 10-15 ma The focus distance varied from 4 to 5 in depend ing on size of the nevus The first radiation dose was calcu lated according to age 500 r up to 1 year 600 r for patients between 1 and 2 years and 700 r in older patients Subsequent treatments were given at intervals of 3-4 weeks and if no re- actions occurred were increased by 100 r to a maximal single dose of 1 000 r which then was repeated after reactions to previous irradiation had subsided When reactions to smaller doses were observed subsequent doses were not increased. Average total dose was 6 000-8 000 r and average duration of treatment 6-18 months In patients with tendency toward pigmentation treatment was interrupted during the summer

Before irradiation the skin was carefully cleaned all scales were removed and the normal skin around the nevus was covered with thick barium applied exactly to the margin of the lesion with a brush Without this preparation pigmented margins developed Large lesions or those located on convex surfaces were subdivided into several areas and irradiated successively The irradiated skin was protected from mechan ical and chemical irritants particularly from ultraviolet light

Complete disappearance of the lesions without telangiec tasia atrophy and pigmentation of the skin occurred in 31 patients. Considerable diminution of red discoloration with few telangiectasias and minimal pigmentation occurred in 35 and disappearance or diminution of red discoloration with considerable atrophy of the skin telangiectasia and pigmen tations in 10 No improvement or deterioration occurred in 6. Superficial bright red nevi were more suitable for the ther apy than were deep ones Better results were obtained in younger patients and with lesions located on the forehead cheeks around the eyes and ear and on the trunk In pa tients with large lesions and with a tendency toward radia

(1) Ceskoslov dermat. 32 156 160 June 1957

necessary to ma ntain immersion for about 1½ hours. The pain is reduced in about 5 minutes and during thi time the patient has rather marked discomfort from the col l water In most cases the pain of the wound i completely relieved within 10-20 minutes. If the extremity i removed from the water before the end of an hour the pa n returns almost to ts original character The wound mu t be explored or an x ray taken to be certain that no spine is retained. In some patient the wound can be explored without anesthesia other than that produced by the cold water Tetanus anti toxin or toxoid should be given if warranted, and an antibiotic should be gi en to decrease incidence of secondary infect on.

Of 18 patients so treated, all had complete relief fr m pain i 10-20 m utes With use of ice packs, 2 patient received only partial relief in 60-90 m nutes A patient who recei ed onl opiates had partial rel ef n 2 hours. The ice pack or ch lled water was not as effect ve a a heavy su pen ion of ice and water

It i thought that the sting ray poison ha a chemical type of action and that reduction of temperature results n reduced absorption from the puncture area. Th may allow the toxin to be slowly released t the circulation and permit ready de toxification by the natural defense forces of the body

C Other Therapy

Action of Emollient Creams and Their Additives. I H Blank[4] (Harvard Med School) defines an emollient as any externally applied material that tends to prevent or counteract dryness of the skin. Most emollients, cosmetic or pharma ceutical are mixtures of an oil and water In addition an emul fyi g agent is used to keep the oil and water well mixed, and perfume may be added. If the oil ha a low melt ng point, the emoll ent feels greasy on the skin f it ha a high melting point, the res dual oily film does not feel grea y Because it does not feel greasy and because as it is rubbed onto the surface its color p obably hanges from white to colorless it seems to vanish.

After emollients are applied to the cutaneous surface som f the water may be taken up by the stratum corneum, but most of it evaporates into th a r The nonvolatile oil of the

(4) J.A.M.A. 64 13 15, May 25 957

in which waves are focused with the aid of a Plexiglas lens, produces mechanical and thermic effects with bulla formation by which e g., verrucae are lifted from the underlying tissues and cast off In 25 of 37 patients verrucae were removed by this procedure in 11 (30%) without scar formation Deep necrosis and persisting pain were unpleasant side effects. In verrucae plantares clavi and in 1 patient with chondrodermatitis helicis circumscripta nodularis chronica *ultrasonic treatment was ineffective it was successful in 1* patient with verruciform interdigital hyperkeratosis.

It is concluded that ultrasonic therapy is of no or little value except for ulceration caused by x ray or radium

Cryotherapy in Treatment of Sting Ray Wounds One of the most excruciatingly painful wounds inflicted on man by any animal is that of the sting ray The sting ray comes into *shallow water when the water is calm and the weather warm.* Generally the victim is a bather wading in the water or a fisherman who is handling one of the rays. Because these rays bury themselves partially in the sand they are usually stepped on by the victim who then has a piercing sensation. Within a few minutes severe pain radiates to the axillary region if the wound is on the hand or arm or to the groin and testis if the wound is on the foot or lower leg

When the ray is stepped on or handled the tail is wielded reflexly and the barb driven into the tissue The direction of the serrated edges allows easy penetration but makes removal of the spine difficult The wound may be a laceration or a puncture. After injury immediate pallor of the skin about the wound is followed by a central hemorrhagic area and peripheral erythema and edema Sometimes there is a black exudate from the barb which remains at the site of injury

The pain is so severe that the most stalwart are apt to have fainting episodes which resemble a mild shocklike state Often shaking chills may be observed within 30 minutes to 2 hours after the attack *if no treatment is given* Some patients show an almost uncontrollable state of hysteria.

J Fred Mullins Charles J Wilson and William C Best[3] (Univ of Texas) treated 20 sting ray victims with cryotherapy The involved extremity is immersed in ice water to a depth of about 6 in above the wound site In most cases it is

(3) South M. J 50 533 535 April, 1957

itamin A ointment alters abnormal keratinization of skin diseases any more than it would be altered by the application of the ehicle alone. Little evidence has been found to show that cosmetics containing itamin A are any more beneficial for controlling symptom of dryness than are simple emol lent not containing vitamin A.

A it seems reasonably well establi hed that estrogen can penetrate normal human kin undesirable sy temic effect from the topical appl cation of estrogen cream might occur However there i a dearth of evidence on the absolute rate of penetration of estrogen through normal and abnormal skin from arious concentrations of estrogen in different types of ehicles. Most estrogen cream currently ava lable do not contain more than 10 000 I U of estrogen/oz. When such cream are used according to d rections, they appear to be free from any abnormal systemic effects

Mu h of the evidence in upport of alteration of the aging kin by local application of estrogen i hi tologic and observed hanges ar difficult to quantitate Much of the work seems to lack objectivity and adequate controls hav seldom been used. Clin cal evidence to support or contradict the opinion that estrogen cream delay or reverse the aging proc ess in th skin meager Any change i likely to be subtle nd to develop lowly and adequate control are important I a recent well-controlled tudy 27 women of variou ages appl ed an estrogen cream to one side of the face and vehicle to the other ide f r 91 days. N difference could be detected in the two sides

► [If one keeps in mind the mechanisms described here by Blank by which creams prevent or alleviate dryness of the skin, it is apparent that relatively simple and inexpensive creams ll achieve this purpose I the era hen the public is bombarded ith such ords as "humectant," it is ell to remember that an appealing aroma, an alluring bouquet, fancy container high price and the power of the spoken ord make for better sales but unfortunately add nothing to the effectiveness of the cream.

I our ow experience such simple and inexpensive preparation 10% sodium chloride (powdered) in Aquaphor (Duke) ha proved beneficial in cases of ichthyosis or extreme dryness and scaliness of the skin This formula as called to our attention by Dr Hyman H Gordon (see also A M A Arch Dermat & Syph 52 178, 1945) The credit for this formula apparently belongs to Ljungstrom (Acta med scandinav 1941) —Eds.]

Barrier Creams Comparative Investigation on Protective Action of Barrier Creams with and without Silicone Oil s eported by W A. Herrmann (The Hague) After 9 d fferent

(Acta dermat venereol 37 276-286, 1957

emollient remains on the skin It has been assumed that the residual oily layer serves as a lubricant Lubrication might be one of the mechanisms by which emollients act, but it does not seem to be the major mechanism It can easily be shown that neither an externally applied oil nor the natural oils can keep the stratum corneum flexible without the aid of water

Application of a film of oil to the cutaneous surface relieves the symptoms of dryness however This film functions in two ways The oil replaces a roughened scaly surface with a smooth film and small spicules of cornified epithelium which extend above the surface and produce roughness are cemented down Thus the cutaneous surface seems smoother More important perhaps if the oily films are occlusive they retard evaporation of water from the cutaneous surface and help to keep the stratum corneum hydrated and flexible

The natural lipid film on the surface is not an occlusive barrier and the major barrier in the skin is below the stratum corneum Since the surface film is not an adequate barrier to prevent loss of water from the stratum corneum and since there is a barrier between the cornified epithelium and the underlying tissues, the cornified epithelium loses water to the environment more rapidly than it receives water from the underlying moist tissues It tends to dry out but fortunately it is a hygroscopic material and does not dry out completely in atmospheres of normal or high relative humidity When the humidity is low as during the winter the stratum corneum may dry out become brittle and break or scale when flexed unless it is adequately protected by a film of occlusive oil Thus the action of the simple emollients i primarily a surface phenomenon and possibly the importance of penetration of the oil into the skin has been overemphasized. An effective emollient mu t be so constituted that it will help the stratum corneum maintain an adequate water content

It is at once apparent that the thicker the tratum corneum the less flexible it will be if it becomes dehydrated If thickening is abnormal because of an added external timulu it may be corrected just by removing thi stimulu but if it is abnormal because of some diseased state and abnormal keratinization correction may be much more difficult There i still little evidence to show that the external application of

water immiscible sol ent was suspected. Cleanser B was an oil-in water emulsion of sarcosinates, sulfonates hexachlorophene, polyethylene liquid petrolatum base no hydrous wool fat Cleanser C contained oil, fatty acid soap propylene glycol titanium dioxide carboxymethylcellulose nonionic type synthetic detergent of fatty amide condensate type par affin wax, soap odorant methyl p-hydroxybenzoate and water

Reactions after use were noted in 20% of patients with acute hand dermatitis with no substantial reduction of this flar reaction after rinsing the cleanser off with cool water or diluted aluminum acetate solution With the chronic phase of hand dermatitis cleansers A and B were more easily tol erated than cleanser C The cleansers were especially u eful f r rapid remo al of some tenacious househol l soils.

In 1709 patients with acne the cleansers were rubbed over the area of invol ement w th avoidance of the corners of the eyes corners of the mouth and neck. After a few moment they were removed w th a washcloth. Residual material was somet me nsed with water During the summer type of residual grease effect was more marked during the w nter dryness was equally pronounced with cleansers A and B The drying effect included redness with desquama tion Seborrheic dermatitis was definitely aggravated by the cleansers, and rosacea was rritated except in hot, hum d weather

Th cleansers were more ffecti e than oils for removal of feces d encrusted medications n infants with diaper der mat t and were effective m preventive routine in infants sceptibl to epeated episodes of diaper dermatitis. Irrita tion occurred in 2% of patients when cleansers A and B were sed In one instance generalized dermatitis followed use f leanser A in a patient with acute diaper dermatitis.

In nfantile eczema and atopic dermatiti the cleansers had limited alue, chiefly removal of tar intment. The drying effect was decreased by additional base usually polyethylene liquid petrolatum mixtures Cleansers A and B were almost iformly irritating on the face

Cleanser B caused no irritation when used as a cleansing agent in otitis externa. It was also used to remove serous and purulent discharges powders and ointments in patients with tasis ulcers, pyogenic ulcerations and cutaneous malignant

barrier creams had been applied to 9 areas on the backs of 20 subjects patches soaked in 2% hydrochloric acid 1% sodium hydroxide solution or 1% sodium hydrochloride solution were applied to these areas and to untreated skin. After 48 hours significantly less local reaction was found in areas previously treated with a water in-oil base with 50% silicone oil or with Kerodex® 71 (a sodium alginate base with fats and excipient) Results were as good with a barrier cream containing 50% silicone oil as with one containing 70% Results with 2 barrier creams of the oil in water type containing 20% silicone oil were no better than with the same cream *without silicone oil A difference in the effectiveness of Kerodex® 71* and 50% silicone oil cream could not be demonstrated.

Tests with fluorescent oil indicated that oil grease and dirt could be more completely and more easily removed from skin protected by an application of Dermotect No. 9 (sodium alginate base with emulsifying agents and fats) or Kerodex® 51 (sodium alginate base with emulsifying agents and fats) These barrier creams were not entirely removed from the skin by contact for 4 minutes with 2 organic solvents (trichlorethylene and white spirit)

Kerodex® 71 and water in-oil base with 50% silicone oil were more effective than a mixture of equal parts of lanolin and petrolatum in protecting the skin of factory workers in contact with 10% sulfuric acid solution Patients with skin lesions presumably due to contact with water or aqueous solutions such as detergents and soda, showed more improvement when using Kerodex® 71 or water in-oil base with 50% silicone oil than when using lanette wax cream with 5% cetaceum as a barrier cream Patients with skin lesions resulting from contact with oil grease dirt paint or organic solvent were better protected by Dermotect no 9 or Kerodex® 51 than by lanette wax cream with 5% cetaceum

► [In our experience barrier creams prove of value only in a small proportion of cases of hand eczema which are aggravated by ordinary wet household activities.—Eds.]

Waterless Skin Cleansers in Clinical Dermatologic Practice Value and Limitations were investigated by Leon Goldman Robert H Preston and Samuel R. Scheen Jr[4] (Univ of Cincinnati) Three cleansers were used in 3 065 dermatologic patients. Cleanser A contained unknown ingredients A wetting agent system with a slight amount of

(4) A.M.A. Arch. Dermat. 76 208-212, August 1957

water immiscible solvent was suspected Cleanser B was an oil-in-water emulsion of sarcosinates sulfonates hexachlorophene, polyethylene liquid petrolatum ba e no hydrous wool fat. Cleanser C contained oil, fatty acid soap propylene glycol titanium dioxide, carboxymethylcellulose nonionic type synthetic detergent of fatty amide condensate type par affin wax, soap odorant methyl p-hydroxybenzoate and water

Reactions after use were noted in 20% of pat ents with acute hand dermatitis with no sub tantial reduction of this flare reaction after rinsing the cleanser off with cool water or diluted aluminum acetate solution. With the chronic phase f hand dermatitis cleansers A and B were more easily tol erated than cleanser C. The cleansers were especially useful for rapid removal of some tenacious household soils.

In 1,709 patients with acne the cleansers were rubbed over the areas of nvol ement, with avoidance of the corners of the yes, corners of the mouth and neck. After a few moments they were removed w th a washcloth. Residual material was sometimes rinsed with water During the summer a type of residual grease effect was more marked during the winter dryness was equally pronou ced with cleansers A and B The drying effect ncluded redness with desquama tion. Seborrheic dermat tis was defin tely aggravated by the leansers nd rosacea was irritated except in hot hum d weather

The cleansers were more effective than oils for removal of f cea d encrusted medications n infants with diaper der matit nd were effect ve in preventive routine in infants suscept ble to epeated episodes of diaper dermatitis. Irrita tion occurred in 2% of patients when cleansers A and B were used In o e nstance, generalized dermatit s followed use f cleanser A n a patient with acute diaper dermatitis.

In nfantile eczema and atopic dermatitis the cleansers had limited value, chi fly removal of tar ointment. The drying ffect was decreased by additional base usually polyethylene l quid petrolatum mixt res Cleansers A and B were almost iformly irritating on th face.

Cleanser B caused no irritation when used as a cleansing agent in otitis externa. It was also used to remove serous and purulent discharges, pow ders and ointments in patients with stasis ulcers, pyogenic ulcerations and cutaneous malignant

ulcerations Initial burning occurred at times but there was no irritation effect

In general waterless cleansers of the cream type are of limited value in clinical dermatology Their uses include removal of tenacious soils in patients with hand dermatitis, cleansing in diaper dermatitis and removal of sticky ointments As in industrial dermatology these materials cannot *always replace conventional cleansers.*

Treatment of Moniliasis with Nystatin. Edwin T Wright, James H Graham and Thomas H Sternberg[7] (Los Angeles) treated 122 patients 42 with oral moniliasis, 17 with vaginal moniliasis and 63 with cutaneous involvement such as paronychia intertrigo and perlèche

Nystatin was applied topically as ointments solutions powders troches capsules and suppositories and jelly for vaginal use The ointment and gel consisted of a plasticized petrolatum base (Plastibase®) containing 5 000-200 000 units of nystatin/Gm ointment The solutions contained 5 000-100 000 units/cc *One solution was propylene glycol and the* other was 2% procaine hydrochloride and 0.25% polysorbate 80 with and without 2 5 mg hydrocortisone/cc The powder contained 175 000 units of nystatin/teaspoon Each troche contained 2 000 units of nystatin in addition some troches contained 2 5 mg neomycin sulfate and 0.25 mg gramicidin *Capsules and tablets used as troches and suppos*itories contained 125 000-500 000 units. The suppositories for vaginal use contained 10 000-100 000 units with some containing an additional 2 5 mg neomycin sulfate and 0 25 mg gramicidin

Among the 122 patients with proved monilia i treated with nystatin lesions healed promptly in 53 slowly in 64 and more slowly in 5 None showed allergic contact dermatitis or primary irritation after treatment Effectiveness was influenced by the vehicle In an ointment on intertriginous areas nystatin gave poor results but in solution it wa rapidly effective The addition of hydrocortisone t the solution shortened the course of therapy

► [There is little doubt that nystatin is often effective yet nonmessy and odorless therapy for monilial infection f the kin and mucous membranes To our knowledge there have been no instances f llergic sensitization to the substance Its bad taste i a di tinct disadvantage in oral monilia —Eds.]

(7) J A M.A. 163 9 93 Jan 12, 1957

Antifungal Antibiotics in Clinical Medicine were stud ed b Harvey Blank[3] (Uni of Miami) The present antifungal a t biotics of greatest alue or promise contain a polyene chromophore chemical group and seem to act by inducing c t ly i of the fungou cell The most promi ing antibiotics all deri ed from streptomycetes are nystatin, trichomycin, amphotericin B and eulicin. Though acti e in vitro and in animals agam t dermatophytes the polyenes topically applied are regularly effecti e only for monilia is in man

Nystatin i the first safe effecti e antifungou antibiotic acceptable for general human use During in est gation n a mals the insolubility of thi antibiotic was a major dif ficulty This characteristic probably accounted for its failure to be absorbed from the ga trointestinal tract and made preparation of a sat factory injectable form impos ible

Nystatin evidently must be appropriately conveyed to the te of clinical infection and in the proper vehicle Vaginal mon liasis g responds best to daily intra aginal nsertion f s ppos tory or ointment for at least 14 day Merely w llowing n statin tablet is not regula ly effecti e in moliasi of th oral mucosa However failure in treatment rare if the drug gets to the lesions in ufficient amounts and for an adequat period each day Occa ional cases may re q ire p to 1 000,000 un t /day an oral su pension in 4-5 d ded doses given after meal to in ure prolonged retention the mouth

Mo lia i of the inframammary axillary nterdigital and anogen tal area can be treated effect ely with shake lotion or du t ng powder contain ng an nt biotic such as nystatin Though ariou st dies failed to demon trat sign ficant mounts of ny t tin blood o r ne after oral adm ni tra tion many pat ent with per i tent and recurrent monili s, where er it may be—vagina, mouth or skin—respon l better nd ma tain remi ion longer if oral admini tration of th ant biotic ccompan es and follows local therapy

Nystatin is an effecti e agent of low toxicity for prevention f moniliasi nd warrants prophylactic admin tration in some patients recei ing broad-spectrum antibiotics, especially the debilitated, the diabet c the premature infant, the pregnant woman and the patient ecei ing cortisone

(3) A M A Arch Dermat 75 84 92, February 957

Treatment of Disseminated Coccidioidomycosis with Amphotericin B Report of Case is presented by Marshall J Fiese[*] (Fresno Calif) Amphotericin B an antibiotic formed by a species of streptomyces has been shown to possess in vivo activity against experimental coccidioidic infections in mice It is similar in action to nystatin but whereas nystatin is not absorbed from the gastrointestinal tract amphotericin B produces detectable blood levels when administered by mouth

Man 27 with severe coccidioidic infection of the face for 7 years, had whole right cheek, right eyebrow nose and lips involved in the inflammation and granuloma. The nose widened, and the sinuses discharged into the nares and mouth and onto the external surface. The lips were thickened and edematous and the voice husky

Amphotericin B was given orally 800 mg every 8 hours. Two days later the edema was subsiding and the lesions showed evidence of drying Treatment was continued for 3 months, the total dose being 200 Gm. Acute inflammation subsided completely Disfiguration from scar tissue was still considerable, but edema disappeared and the sinuses healed There were no symptoms suggesting toxicity though the cephalin flocculation and thymol turbidity test reactions became mildly abnormal

Mycetoma Pedis Four Cases Treated with Streptomycin are reported by L Ziprkowski G Altmann F Dalith and U Spitz[1] (Tel Hashomer Israel) All 4 patients were immigrants from Yemen and in 3 the infection was definitely acquired in that country The other patient had been in Israel 9 years before signs of infection appeared In 2 the causative organism was Nocardia madurae in the third culture did not reveal the causative agent but the clinical picture biopsy and morphology of grains were very similar to those in the first 2 In the other patient Streptomyces somaliensis was cultured

X ray examination showed marked swelling of the soft tissues in all patients Typical changes in the tarsal bones were found in 3 and an elevated eosinophil count in 4 However as a high percentage of Yemenites show elevated eosinophil count due to schistosomiasis no conclusion can be made regarding the correlation between mycetoma and increase in eosinophils.

Treatment in all consisted of large doses of streptomycin Complete recovery occurred in 2 In 1 treatment had to be stopped after 40 Gm because a severe psychosis developed

(*) California Med 86 119-120, February 1957
(1) A.M.A. Arch. Dermat. 75 855-863 June 1957

but definite improvement could already be observed. The other patient, who received 134 Gm streptomycin and was discharged in good condition, 5 months later had a minor relapse which responded to treatment with streptomycin and chlortetracycline. In view of these encouraging results, it is suggested that streptomycin be tried in all cases of mycetoma pedis before radical surgical intervention.

Acrodermatitis Enteropathica. This condition usually begins early in childhood. It is characterized by a symmetrical eruption most prominent on the face, nape of the neck, buttocks, genitals, elbows, knees, hands and feet. The lesions



Fig. 2.—Symmetrically distributed rash on skin of 8-month-old infant. (Courtesy of Danbolt, N.: Acta dermat.-venereol. 34: 257-271, 1954.)

are irregularly erythematous weeping areas, usually vesiculopustular, particularly at the periphery. Other manifestations are blepharitis, paronychia, atrophy of the nails, total alopecia, erosions of the buccal mucosa and bouts of diarrhea. The disease runs a prolonged course; growth is retarded and the general condition is bad. Niels Danbolt (Univ. Hosp., Oslo) reports on 2 patients in whom treatment with Diodoquin was beneficial. The first began to improve after several months' treatment and finally became symptom free. Case 2 is presented.

Girl, aged 8 months, had irregular weeping patches of dermatitis on the face, nape of the neck, buttocks, inguinal areas, genitals, flexors of elbows, hands, knees and feet (Fig. 2). There was a marked pa

(3) Acta dermat.-venereol. 34: 257-271, 1954.

onychia, with discoloration and atrophy of the nails, and total alopecia. She had chronic diarrhea and general condition was poor Symptoms had started 1 month after birth.

Treatment consisted of 210 mg Diodoquin[*] 3 times daily with cortisone and Achromycin from time to time After 2 months, the rash had practically disappeared, but the general condition remained poor Extensive pneumonia developed and she died.

Autopsy revealed a series of erosions in the large intestine and pneumonia. Microscopic examination showed granulation tissue of a nonspecific, subacute type

As Diodoquin[*] is not absorbed into the blood stream when taken orally its favorable effect in acrodermatitis enteropathica must depend on its direct pharmacodynamic action on the inflammatory process in the intestinal wall It not only restores the intestines reabsorptive capacity to *normal as indicated by weight gain and growth but also* activates an intrinsic factor which presumably plays a part in maintaining the skin s resistance capacity and hair growth

Acrodermatitis enteropathica often affects several members of a family Although a congenital predisposition undoubtedly exists some unknown provocative factor is probably necessary for the disease to develop in its entirety

► [The question arises whether the lesions in the intestines were the sites of the primary process with the cutaneous changes being secondary manifestation or whether the intestinal and cutaneous changes both resulted from the same underlying (and unknown) cause. The fact that Diodoquin (which is not absorbed through the intestinal wall) is effective treatment in many cases favors the former theory —Ed]

Acrodermatitis Enteropathica in an Adult is reported by Edmund L. Piper[3] (Dartmouth Med School)

Woman, 46 had marked thinning of the hair over the frontoparietal areas. She had had dermatitis of the fingers toes and face with total alopecia, anorexia, weight loss and mucoid stools at age 7 Remission had followed oral therapy with bismuth and arsenic. A recurrence at age 19 also responded to this treatment. Since then she had had mild exacerbations every few months, and a severe episode had not responded to treatment for about a year

Axillary and pubic hair was scant. Masklike dusky red scaling dermatitis stuckled with pustules involved the entire face and external ears. Angular stomatitis (Fig 3) and blepharitis were present The tongue was swollen, deeply furrowed and covered with a smooth white film. Scaling erythematous dermatitis involved the perianal area, and shallow bullous lesions with crusted hyperkeratotic roofs involved the digital paronychial areas, heels, ankles and an elbow The distal palmar and plantar surfaces were hyperkeratotic longitudinally fissured and peeling She had frequent mucoid stools and anorexia.

(3) A.M.A. Arch Dermat. 76:221-224 August 1957

Candida albicans was cultured from a paronychial lesion, the angular stomatitis and a stool. Microscopic study of a hyperkeratotic verrucous lesion revealed intraepidermal vesicle formation, marked hyperkeratosis and parakeratosis. Benign dyskeratotic cells were present in the stratum corneum. Examination of a bullous lesion revealed suprabasal separation, with the blister fluid containing single and clumped prickle cells, neutrophils and eosinophils. A pustule showed superficial epithelial inclusion cyst containing cambolyte-like or dyskeratotic prickle cells and an inflammatory exudate.

Diiodohydroxyquin (Diodoquin) was administered orally 650 mg 4 times a day. Improvement of the skin lesion was noted within a week. Passage of mucoid stools ceased immediately. After 3 weeks

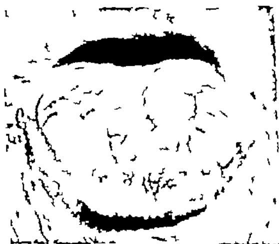


Fig. Angular stomatitis and swollen furrowed tongue. Courtesy of Paper. F. L. A.M. Arch. Dermat. 121:22, August 1957.)

all skin lesions healed. New hair growth, weight gain and voracious appetite were noted. With continued administration of the drug she was well when re-examined after 9 months.

The salient differentiating features of acrodermatitis enteropathica are (1) gastrointestinal disturbances with mucoid stools, (2) partial alopecia, (3) periorificial dermatitis, (4) bullous lesions not preceded by trauma, (5) frequent cutaneous moniliasis and presence of C. albicans in the stools, (6) response to diiodohydroxyquin and (7) a distinctive histopathologic picture. A familial tendency has often been reported.

Although it is true that the severer cases terminated fatally before use of diiodohydroxyquin, this case suggests that

onychia, with discoloration and atrophy of the nails, and total alopecia. She had chronic diarrhea and general condition was poor. Symptoms had started 1 month after birth.

Treatment consisted of 210 mg. Diodoquin® 3 times daily with cortisone and Achromycin® from time to time. After 2 months, the rash had practically disappeared but the general condition remained poor. Extensive pneumonia developed, and she died.

Autopsy revealed a series of erosions in the large intestine and pneumonia. Microscopic examination showed granulation tissue of a nonspecific subacute type.

As Diodoquin® is not absorbed into the blood stream when taken orally, its favorable effect in acrodermatitis enteropathica must depend on its direct pharmacodynamic action on the inflammatory process in the intestinal wall. It not only restores the intestines' reabsorptive capacity to normal, as indicated by weight gain and growth, but also activates an intrinsic factor which presumably plays a part *in maintaining the skin's resistance capacity* and hair growth.

Acrodermatitis enteropathica often affects several members of a family. Although a congenital predisposition undoubtedly exists, some unknown provocative factor is probably necessary for the disease to develop in its entirety.

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(3) A.M.A. Arch. Dermat. 76:221-224, August, 1957.

tion patient failed to show any abnormalities. It is fascinating to think that the same drug could have entirely reverse effects in one and the same disease. However there are other examples of such opposite effects produced by the same compound, e.g. the same agents that have excellent photo-protective properties can also act as photosensitizers. With sulfonamides this is of frequent occurrence, whereas para-aminobenzoic acid photosensitizes relatively infrequently.—Eds.]

Plaquenil Sulfate in Treatment of Lupus Erythematosus and Light Sensitivity Eruptions. Plaquenil sulfate is a 4-aminoquinoline antimalarial preparation differing from chloroquine diphosphate in that one of the terminal ethyl groups on the tertiary amino nitrogen is replaced by a hydroxyethyl group. Dosage is 0.2-0.8 Gm. daily.

James H. Bennett and Rees B. Rees (Univ. of California) treated 25 patients with lupus erythematosus and light sensitivity eruptions with Plaquenil sulfate for 3 weeks to 6 months. Among 14 patients with lupus erythematosus (13 chronic discoid and 1 subacute) good results were obtained in 9, improvement in 2 and no benefit in 3. In 4 patients with good results, Plaquenil® was the only antimalarial tolerated or the only one effective. Two who received no benefit from Plaquenil® had found quinacrine, chloroquine and amodiaquin effective. Minor side effects occurred in 4 patients and included nervousness, toxic eruption, intestinal cramps and hoarseness.

All patients who received Plaquenil had also taken chloroquine. With chloroquine, 9 had good results, 2 were improved and 3 had no benefit. Minor side effects occurred in 8 of the 14 patients. Of 8 patients who had received quinacrine 4 had good results, 1 was improved and 3 had no benefit; of 7 who had received amodiaquin 5 had good results.

Among the 11 patients with light sensitivity eruptions receiving Plaquenil, the lesions cleared in 3-5 weeks in 5 patients and 4 others were improved. One patient in whom the lesions cleared had not responded to chloroquine or quinacrine. Among 5 patients who had taken chloroquine, the eruption had cleared in 2 and improved in 1. Two patients had also received quinacrine with no benefit.

Plaquenil appeared to be as effective as chloroquine in treatment of lupus erythematosus and light sensitivity eruptions and had fewer side effects. The main advantage of Plaquenil® was that in 5 patients it was the only antimalarial

(5) A.M.A. Arch. Dermat. 75: 11-113, February, 1957

milder forms of the disease may persist well into adult life with spontaneous exacerbations and remissions Acantholytic like prickle cells in the lesions have not been previously noted in acrodermatitis enteropathica

► [The clinical features of this case together with the response to Diodoquin® tend to support Piper s contention that this patient has an adult form of acrodermatitis enteropathica. On the other hand, the absence of the disease in infancy and early childhood speak against this assumption. Perhaps the case would fit in better with the syndrome of systemic moniliasis which has been seen in adults.

Over the years, numerous forms of therapy intended to produce intestinal antisepsis have been tried in various dermatoses. The successful management of Piper s case and of acrodermatitis enteropathica with diiodohydroxyquinoline is an excellent example of therapeutic effects achieved by a drug that presumably is not absorbed through the intestinal mucosa. Therefore, the benefit which occurs in organs and tissues distant from the intestinal tract must be attributed to destruction or alteration of intestinal micro-organisms or their metabolic products or to alteration of the bowel contents or to an effect on the anatomic structure, physiologic function or biochemical activity of the intestinal wall.—Eds.]

Porphyria Cutanea Tarda Report of Case Successfully Treated with Chloroquine is presented by Irving D London[4] (Montgomery Ala)

White man 47 had numerous excoriations and lichenified papules on wrists, hands and the right cubital space. Later several lesions were noted on the cheeks and forehead. The eruption had been present for 2 years. Histologic changes were compatible with epidermolysis bullosa, but the pathologist suggested that porphyria cutanea tarda should be ruled out. Examination of the urine under Wood s light revealed fluorescence. Ehrlich s reagent indicated presence of porphobilinogen. The urine turned dark on standing The bromsulfalein test was within normal limits. Blood counts were normal.

Steroids and vitamins were not beneficial. Almost immediate improvement was noted on 0.25 Gm chloroquine twice daily After 7 weeks, the dose was reduced to 0.25 Gm. once a day No new lesions appeared after chloroquine was started. After 5 months, the dose was reduced to 0.25 Gm. every other day with the medication occasionally omitted for a week. Treatment was stopped entirely after another 5 months. When he was examined again 2 months later the skin was still clear Urine studies showed coproporphyrin, negative uroporphyrin, negative porphobilinogen, positive no color change after standing 24 hours.

Treatment of acute and chronic porphyria has been unsuccessful The present report is apparently the first in which prolonged relief was effected in porphyria cutanea tarda with complete remission of bulla formation after treatment with chloroquine.

► [Contrary to the 2 case reports in the article by Davis and Vander Ploeg (see this Year Book, p. 150) the investigations of liver function in Lon

(4) A.M.A. Arch. Dermat. 75:401-403 June, 1957

don patient failed to show any abnormalities. It is fascinating to think that the same drug could have entirely reverse ffects in one and the same disease. However there are other examples of such opposit ffects produced by the same compound, g the same agents that have excellent photo-protective properties can also act as photosensitizers. With sulfonamides this is frequent occurrence whereas para-aminobenzoic acid photosensitizes relatively infrequently.—Ed.]

Plaquenil Sulfate in Treatment of Lupus Erythematosus and Light Sensitivity Eruptions. Plaquenil sulfate is a 4-aminoquinoline an antimalarial preparation differing from chloroquine diphosphate in that one of the terminal ethyl groups on the tertiary amino nitrogen is replaced by a hydroxyethyl group. Dosage is 0.2-0.8 Gm. daily

James H Bennett and Rees B Rees (Univ of California) treated 25 patients with lupus erythematosus and light sensitivity eruptions with Plaquenil[a] sulfate for 3 weeks to 6 months Among 14 patients with lupus erythematosus (13 chronic discoid and 1 subacute) good results were obtained in 9 mprovement in 2 and no benefit in 3 In 4 patients with good results, Plaquenil was the only antimalarial tolerated o the only one effective Two who received no benefit from Plaquenil had found quinacrine, chloroquine and amodia q ffective. M nor side effects occurred in 4 patients and ncluded nervousness, toxic eruption, intestinal cramps and hoarseness

All patients who rece ed Plaquenil had also taken chloroquine With chloroqu ne 9 had good results 2 were improved and 3 had no benefit. M nor side effects occurred in 6 of the 14 pat ents. Of 8 patients who had rece ed quinacrine 4 had good results, 1 was improved and 3 had no benefit of 7 who had received amodiaquin 5 had good results.

Among the 11 patients with light sensitivity eruptions recei ing Plaquenil the lesions cleared in 3-5 weeks in 5 patients and 4 others were impro ed. One patient in whom th lesions cleared had not responded to chloroquine or quinacrin Among 5 patients who had taken chloroquine, the eruption had cleared in 2 and improved in 1 Two patients had also recei ed quinacrine with no benefit.

Plaquenil appeared to be as effective as chloroquine in treatment of lupus erythematosus and l ght sensitivity eruptions and had fewer side effects. The main advantage of Plaq enil[a] was that in 5 patients it was the only antimalarial

(7) A.M.A. Arch. Dermat. 75:18, 93 February 1957

preparation that was effective and that was tolerated

► [Our experience is similar to that of the authors. Each of the antimalarials, quinacrine, chloroquine and Plaquenil® has its place in management of lupus erythematosus and light sensitivity eruptions. Where one is effective in a particular case, another may fail where one is well tolerated by the patient, another may produce side effects (these differ considerably in kind and degree)

Effective daily doses for these three drugs vary but generally fall within this range

Quinacrine (Mepacrine, Atabrine®)	100-300 mg
Chloroquine (Aralen Aviaquine)	250-750 mg
Plaquenil®	400-1,200 mg —Eds.]

Treatment of Lupus Erythematosus and Lymphocytic Infiltration of Skin with APA 5533 is described by Charles R. Rein and Raul Fleischmajer[6] (New York) About three fourths of the patients with either of these conditions respond satisfactorily to mepacrine chloroquine or Plaquenil® Some respond better to one drug than to another and each drug produces some side effects Efficacy of APA 5533 which is a combination of these drugs was investigated in 10 patients with chronic *discoid lupus erythematosus and in 4 with* lymphocytic infiltration of the skin One tablet of APA 5533 contained one fourth of the usual dose of each antimalarial mepacrine 25 mg Plaquenil® 50 mg and chloroquine 65 mg Most patients were started on 2 tablets 4 times a day As soon as there was definite evidence of improvement the daily dose was reduced by 2 tablets at 2 week intervals until a minimum maintenance dose was determined. When pronounced side effects occurred treatment was discontinued until evidence of intolerance subsided and then resumed at one half the original dose

Of the 10 patients with discoid lupus erythematosus 7 obtained an excellent result In 3 there was no response to a daily dose of 8 tablets but when the dose was increased to 12 tablets excellent improvement occurred Two patients remained clear even on a maintenance dose of 4 tablets daily and 1 had recurrence with the decreased dosage Of 4 patients with lymphocytic infiltration of the skin in 3 complete clearing occurred and 1 showed slight improvement Two patients had severe diarrhea vertigo and muscle pain on a dosage of 8 tablets daily One had no side effect at this dose but severe diarrhea developed when 12 tablets were taken daily The other 11 patients had no side effects or had

(6) Brit. J Dermat 69 174 177 May 1957

only minimal discomfort consisting of mild diarrhea diplopia, nausea or vertigo. Six of these patient had had marked ide effects from previous antimalarial regimens

Treatment of Creeping Eruption with Chloroquine Diphosphate Preliminary Report is made by James W Burks Jr and Frederick A. J Kingery[1] (Tulane Univ) Of 1? patient with typical clinical manifestation of larva m gran ll but 2 howed complete clinical in olution or definite re gres ion f the dise e within 2 weeks. The failures oc urred i young children who did not take the drug regularl

Dosage of chloroquine wa 0.25-0.5 Gm orally twice da ly for 10 days n adult and 0.125 Gm. twice daily in children. S nce the cou se of creeping eruption aries from se eral week to many months it appear that chloroquine therapy ign ficantl hortened t The mechan m by wl ich favorable result are produced must await further study

New Data on Mechanism of Action of Atabrine are um mari ed by E N gy L Kocsár I J kav C H dházy and K Tur (U of Debrecen) The trik ng ant inflamma tory effect f Atabri e are w ll known to clinicians from the therapeutic result achieved n acute and h on c lupu erythematosus, l ght dermatoses and pemph gu Previous att mpt to naly e it effects corroborated t antihi ta minic ction

A mal periment t determine whether Atabr ne has) ffect on a lethal dose of histam ne revealed that cats p t eated w th th drug rvi ed wherea co trol an mals died within a f w minutes after th h tam wa dm is tered tra enou ly The Atabrine effects could not be ex plained by ncreased ant histaminase ction Homogenat f pulmonary t sue f gu nea pig and rat howed the same rate f h tam ne d sintegration (i e no infl ence f h tamitnase tiv ty) wh ther At brine[1] w s gi en as prel minary t tment t living animal added to pulmonary ti ue after the an mal d ed or not at all (control an mal) Animal t eated w th Atabrin howed considerably (nearly 30%) increased secretion of 17 ketosteroid and markedly hea ier drenal

Sections stained w th hematoxylin-eosin revealed distinct hypert ophy of the adrenal cortex. Lipid staini g displayed

[1] South M J 49 290 292, November, 1956
Dermatologica 1 3 98, August, 1957

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(6) Brit. J. Dermat. 69: 174-17?, May, 1957.

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[7] South. M J 49 1290 1292, November, 956.
[8] Dermatologica 1 4 144, August, 957

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(6) Brit. J Dermat. 69 174 17 May 1957

Much work remains to be done however in evaluating time and dose relations for patients of various complexions For the present, the drugs can be used only in a limited closely supervised, experimental way in patients intelligent enough to be trusted with them The risk cannot be ruled out at this time that the drugs may increase not only the protecti e responses to sunlight, but also the carcinogenic response.

► [Great caution must be exerted at the present stage of knowledge before concluding that the drug taken systematically can protect the skin of those unable to tan against the possible development of skin cancers. A Arnold cautions, one must make certain that the drugs do not increase response of the skin to the carcinogenic action of sunlight.

In small percentage (15%) of patients with vitiligo, 8-methoxypsoralen has proved of distinct benefit in returning pigment. Although topical applications may be more effective in some cases, as well as being cheaper systemic administration, in our experience, is simpler and does not cause the sometimes severe local reactions that follow topical use of the 8-methoxypsoralen solution. This is particularly true when many small scattered lesions must be treated.—Eds]

Safety Record of BCG Vaccination and Untoward Reactions Observed after Vaccination. According to Ole Horwitz and Johannes Meyer[1] (Finsen Inst., Copenhagen) compli cations may be nonspecific and specific Nonspecific complications are chiefly k loid, eczema, epithelial cysts and gran uloma in the vaccination ulcer Occasionally such disorders may ha e to be differentiated from specific complications occurring at the vaccination site. Specific complications may be local regional or generalized. The local complication of greatest importance is lupus vulgaris. Others include large and/ r prolonged ulceration, subcutaneous abscess, scrofu loderma, lymphangitis tuberculid, tuberculosis verrucosa cutis and Koch s phenomenon. The most frequent regional complication is adenitis.

A total of 9 cases of generalized BCG tuberculosis, includ ing 4 fatal cases has been reported. The number of BCG-accinated persons all over the world is estimated to be about 70,000,000-100,000,000. Considering this great number the severe complications, generalized cases and lupus, are apparently extremel rare. In the Scandinavian countries, where the 4 fatal cases occurred, about 4,000,000 BCG vac cinations have been made Because of the excellent medical facilities in these countries it is improbable any other (un eported) cases hav occurred. However many countries

(1) Advances Tuberc. Res. 8:245-271, 1957

in control animals the various changes of the cortical cycle, such as phases of secretion transition and discharge, whereas in Atabrine* treated animals the cells of the zona glomerulosa and fasciculata were lipid positive, corresponding to the secretion phase.

These findings indicate stimulation and hypertrophy of the adrenal cortex with increased production and mobilization of cortisone. The anti inflammatory effects of Atabrine* may be due partly to hyperfunction of the adrenal cortex and mobilization of cortisone Apart from antihistaminic effects other obscure factors should be considered.

► [In our experience with Atabrine* and related agents for the treatment of chronic discoid lupus erythematosus and other dermatoses, nothing has been seen in the way of side effects which would suggest a corticotropin-like or corticosteroid-like action of this drug However it had been suspected by some dermatologists that the effect of Atabrine* and related agents is due to stimulation of the adrenal cortex. These studies, to our knowledge, are the first which objectively show there is actually an anatomically demonstrable enlargement of the adrenals under Atabrine* therapy —Eds.]

Psoralens and Sun Tan Augmentation of Skin Responses to Sunlight by Psoralen Derivatives is reported by Harry L. Arnold Jr[9] (Honolulu) Experimental studies on volunteers who sunburned easily indicate that 8-methoxypsoralen and 8-isoamyleneoxypsoralen augment the tanning and corneal thickening normally produced by sunlight. They also augment sunburn response shortening the time required for its production and other things being equal increasing its intensity and duration. The tan acquired may be of slightly different color or quality and perhaps more persistent than ordinary tan These drugs will in many cases though probably not in all cause reappearance of melanin in areas of vitiligo This response is slow and uncertain and cannot be highly recommended except for cases of relatively limited extent and short duration Topical application seems more practical than oral and is less expensive.

Probably the chief value of these psoralen derivatives lies in their ability to facilitate sun tanning This would have two advantages. Persons able and eager to acquire a tan could get one and maintain it without inflicting so much permanent damage on underlying connective tissue And more important, persons unable to tan and subject to skin cancer probably could be largely protected against this disorder

(9) Hawaii M. J 16 391 395, Mar Apr 1957

1 year in those under 20 to 47.5% of those 70 or over

Generalized herpes zoster occurred in 11 patients in 3 of whom there was lymphoma. Extensive gangrenous changes ppeared in 3. The commonest associated diagnosis was lymphoma, which wa made in 4.2% of all patients.

The trigeminal area wa involved in 16.3% of patients The postherpetic neuralgia was consistently longer in this group and severe complications were commoner in the acute phase of the disease Eye enucleation was necessary in 2 pa tients and complet vision loss occurred in 2.

Different types of treatment used during the acute and chronic phases of the process did not mod fy sub tantially th natural course of the disease In the severest ca es vari ous urgical procedures w th the goal of producing a perma ent block the pain bearing nerve fibers were of little benefit.

► [A ery orthwhile summary that makes clear the need for therapeutic methods to control postherpetic neuralgia. It should be pointed out tha the cases reviewed ere seen during 1933-49 Modern drugs, g. ACTH and the corticosteroids, fortunately hav been of some help in relieving the discomfort of this affliction

During the acute phase, gamma globulin and more recently emetine have been recommended. (See he following 2 articles) —Eds]

Treatment of Herpes Zoster with Emetine. During 1955-57 V J rda J Lenf ld and L Rothsch ld[3] (Palacky Univ) treated 40 herpes zoster patients with emetine The intercostal n rve was involved in 20 patients, the trigeminus n 15 th cerv cobrachialis in 3 and the ischiadicopopl teal in 1 Intramuscular njections of 40 mg emetine were given on th 1st, 3d and 5th day During 1950-56 another group of 40 control were treated with Aureomycin penicillin sym pathölytic drugs and vitamins.

Pai ceased in 5-7 hour after the first njection in all but 2 pat ent with gangrenous lesion The a erage duration of the disease from onset of ymptoms to complete cure was 10 3 day n patients u der age 40 and 13 days in those older compared with 20 nd 33 3 days in the ontrols. The a er g d ration of the ll ess after initiation of emetine therapy was 3 4 days in the younger and 5.f days in the older patients Postherpetic neuralgic pain occurred in 32.5% of the con trols, but in none of the patients treated with emetine. No complications were encountered.

To lucidate the mechanism of emetine action its pos ible

3) Ceskoslov dermat 32 349 13 1957

where large-scale vaccinations have taken place do not have similar good facilities. Many of even the severest complications may have occurred without notification of public health authorities. Calculated from the frequency in Scandinavia, it is possible that 70 cases of fatal BCG tuberculosis may have occurred throughout the world.

Examination of preschool children in Denmark 12-16 months after BCG vaccination revealed an incidence of perforating adenitis of 2%. The frequency was highest among young children. When reservation is made with regard to the long incubation period and the late diagnosis of lupus vulgaris, the frequency is 1 case/100 000-175 000 vaccinated persons.

Many factors seem to suggest that the frequency of all complications depends among other things on the dose and virulence of the vaccine and, in lupus, on the tuberculin allergy of the vaccinated person. Thus, by keeping the dose and virulence of the vaccine within reasonable limits and by a more thorough tuberculin testing, especially of persons to be revaccinated, it may be possible to reduce the frequency of complications without impairing the protective effect of the vaccination.

When it is considered that large-scale vaccination may gradually prevent occurrence of several hundred fresh cases of tuberculosis annually, the complications in the frequencies recorded are not significant. However, knowledge of complications may cause some persons to refuse to be vaccinated. Complications cannot be considered a contraindication as long as tuberculous infections have not become extremely rare.

► [The small incidence of fatal, serious and nonserious complication of BCG vaccination cannot detract from the great benefits that has been derived from this form of preventive treatment.—Eds.]

Outcome of Patients with Herpes Zoster. Jose M. de Moragas and Robert R. Kierland[2] (Mayo Clinic and Found.) reviewed the records of 916 patients with herpes zoster and postherpetic neuralgia. *Age and localization (trigeminal)* were the only factors that seemed to affect prognosis. The percentage of patients with pain increased with age. Pain occurred in 16.7% of patients under age 20 and in 91.3% aged 70 or over. The duration and severity of postherpetic neuralgia increased from 4.2% of patients with pain for more than

(2) A.M.A. Arch. Dermat. 75:193-196, February, 1957.

significant variation from normal in psoriasis. However di rect studies of pancreatic enzyme contents in the duodenum in patients with psoriasis have not been performed in this country. A single partial study of 12 patients in the German literature reported lowered pancreatic amylase and trypsin in psoriasis.

The authors analyzed exocrine pancreatic fluid obtained by duodenal intubation of 30 patients with psoriasis and 10 normal controls. No significant difference in the pancreatic enzyme levels was found. On the basis of this study pancreatic enzyme replacement therapy would not seem indicated.

Pancreatic Extracts in Treatment of Psoriasis: Evaluation of Entozyme and Lipan. In the past 5 years there has been ncreased nterest in use of pancreatic extracts in treatment of psoriasis. The rationale for use has rested on the premise there is deficiency of pancreatic enzymes in patients with psoriasis thereby resulting in incomplete digestion of fats. However in a comprehensive review of the literature, Eugene M. Farber and Harold M. Schneidman (Stanford Uni) were unable to find evidence to support this premise. They undertook a controlled double blind study using pancreat c extract (Entozyme® and Lipan) and a placebo to determine the efficacy of pancreatin in treatment of psoriasis.

Of 61 patients, one-third used no topical therapy or only petrolatum. Of the others, some were kept on their previous regimen and some were gi en tar or mercury preparation for topical use. The observation period was 6-18 weeks and the dose aried from 3 to 9 tablets daily. Improvement in the pat ents taking pancreatic extract was not greater than in those taking placebos.

A questionnaire answered by 28 dermatologists who had used Lipan or Entozyme® in psoriasis cases showed that 24 had not noted improvement and 4 had noted minimal impro ement.

► [The findings reported and the conclusion drawn in the previous article that pancreatic enzyme replacement therapy would not be expected to benefit psoriasis, is borne out by the results achieved with Entozyme® and Lipan. This has been our experience, also, with the same pancreatic extracts.—Eds.]

Personal Experience with Tetrahydrofurfurylic Ester of Nicotinic Acid in Alopecia Areata. According to Enrique E. Tello (Univ. of Córdoba) the three principal causes of alo-

(8) A.M.A. Arch. Dermat. 74:[illegible], August, [illegible]
(9) Arch. [illegible] dermat. 7:31-35, March, [illegible]

analgesic effect was studied in mice and its anti-inflammatory effect was studied in rats. Its analgetic effect could not be demonstrated; however, strong suppression of local inflammatory reaction was observed after injection of 2% formaldehyde in rats. The anti-inflammatory effect of emetine was found to be greater than the anti-inflammatory actions of phenylbutazone, cortisone and quinine which were studied in identical experiments.

► [Emetine is a highly toxic drug unless carefully used within certain definite dosage limits. Ordinarily not more than 1 mg./kg. body weight, up to 60 kg., should be given daily and then not for more than 10 days. And this dose should not be given to markedly debilitated or otherwise ill patients.—Eds.]

Herpes Zoster and Emetine Hydrochloride. Impressed by therapeutic results previously reported by Griveaud, Achard and Morin (1953), Luiz Bastos Viegas and Luiz Cunha Viegas[4] (Porto, Portugal) administered emetine hydrochloride to 31 patients. Subcutaneous injections (2-6 cg.) were given daily for a maximum of 5 days. The dose varied according to age and weight and treatment was withdrawn on cessation of pain.

The results were excellent in all but 1 patient. Pain disappeared in 12 hours to 3 days, progression of lesions was arrested after the 1st or 2d injection and involution of vesicles occurred within 6 days maximum. In 1 extremely severe case general antibiotic therapy was administered simultaneously in an effort to avoid infectious complications. In 2 patients who already had pain admitted during the early period, vesiculation was prevented. Side effects, consisting of nausea and vomiting, occurred in only 1 patient.

Local applications of various types were used in these patients with no discernible difference in development of vesicles. Hence the authors conclude that these drugs are not of primary importance when emetine hydrochloride is used.

Exocrine Function of Pancreas in Psoriasis was studied by Eugene M. Farber, Rolf E. Johnsen (Stanford Univ.) and Harry Shwachman[5] (Harvard Med. School).

During the past 25 years a number of reports have suggested that psoriasis is induced or aggravated by altered exocrine pancreatic function. Indirect measurement of pancreatic exocrine function through study of fecal nitrogen, fecal fat, serum lipase and serum amylase levels has revealed no

(4) Ann. dermat. et syph. 84: 400-405, July-Aug., 1957.
(5) A.M.A. Arch. Dermat. 76: 236-238, August, 1957.

ta in these respects. Even when local irritation was produced, it receded as soon as the treatment was discontinued and it did not prevent the subsequent renewal of the applications

Th results were s follows m 53.96% the plaques wer co ered with hair within 1 month in 16.66% they were cov ered within 2 months and in 11.98% they were covered within 3 months. These figures show that Trafuril is the medicament of choice for topical application in ord nary alopecia areata

► [It appears unwise to speak of principal causes of alopecia areata, ince herein many possible causes have been blamed, none ha been proved The etiology of this disease remains an enigma and in most instances hair regrow for unknown reasons and without benefit of treatment. When it regrows, it often does so ithin 1 3 months Therefore, without control studies it appears impossible to draw any conclusions regarding the benefit of Trafuril[1] therapy Also it ould be important to know what percentage of cases of more than 1 year duration ere benefited.—Eds.]

Present Treatment of Skin Tuberculosis is outlined by Claude Huriez and Pierre H. I kee[8] (Lille) who anal zed 369 patients treated during the past 15 years in northern Fra ce One th rd of those with tuberculous lupus were cured by Charpy treatment with ergosterol (vitamin D_2) alone In 55% cure was btained by alternating antibiotics and itamin D_2. Th present use f isoniazid, streptomycin and itam n D_2 has extended the cure rate in all types of lupus

Ski t berculosis other than lupu which is only slightly espon i e to tamin therapy greatly benefited by ant bi-tics, includi g isoniazid The healing rates in inoculation bancre were 80% m errucous types, 100% and in vegetati g ulcerous nd gummatous types, 75 % Only 55% of the scrofulodermas were cured, despite local injections of isoniazid Large doses of vitamin C remain useful in Bazin s disease In som cases cures were effected by nonspecific anti biot suggesting the presence of benign pyococcic lesions n th hypoderm

In any type of skin tuberculosis mixed antibiotic therapy hould be dministered consisting of perfusion of isoniazid, dihydrostreptomycin and para minosal cyli acid T eat ment should be prolo ged for at least a year and vitam n D hould be given as an adjunct

Experimental studies showed that massive doses of vitam n D_2 ha e an almost cortisone-lik effect. Cortison ther py combined with antibiotics proved effective in 20 cases of

(8) Semaine hôp Paris 33 171-180, Feb 4, 957

pecia areata are focal infections endocrine disturbances and psychogenic factors such as emotional tension fatigue and shock Many forms of treatment have been advocated each designed to combat one or more of the presumptive causes of the disease. Sometimes however if the precise cause cannot be determined or even if it is known additional treatment with local rubefacients may be needed to overcome the underlying vascular spasm to which the alopecic plaques have been attributed No treatment produces uniformly satisfactory results and in some cases no medicament or combination of medicaments succeeds in stopping the progress of the disease or in stimulating the regrowth of hair on the initial plaque

The tetrahydrofurfurylic ester of nicotinic acid (Trafuril*) possesses local hyperemia producing properties when rubbed on the skin Also its action is transmitted by the reflex pathway to the deeper lying organs and tissues (Head's reflex zones) These effects which are nullified or impeded if the temperature of the skin is below normal seem to be exerted directly on the blood vessels rather than indirectly by way of the H substance Erythema appearing in 3-18 minutes and lasting for ½ hour or more is accompanied by a feeling of warmth and sometimes by itching The topical use of this substance is thus indicated in all dermatologic conditions responding favorably to an increase in the blood circulation

The author first reported the effect of tetrahydrofurfurylic ester of nicotinic acid on alopecia areata in 1952 The present study deals with the results obtained in 126 patients (100 males) aged 5-52 all of whom had ordinary alopecia areata. None had any foci of infection or endocrine disorders that were clinically apparent or that could be detected by laboratory studies nor were there any in whom psychogenic factors could be considered operative No changes were made in diet or in manner of living In all the condition had been present from 15 days to 15 months and in most other forms of treatment had been tried without success

The patients were instructed to use a 5% solution of Trafuril* rubbing it into the scalp for 5 minutes 3 times a day Those who wished to increase the number of applications and the time of friction were free to do so Signs of local irritation appeared only in those who exceeded reasonable lim

eral hypotension with orthostatic values lower than the clinostatic values seen in some of the patients suggested that, besides its chemotherapeutic action the drug may have a pharmacologic action on the peripheral vessels

► [Our own experience with Marsilid in the treatment of psoriasis has been unfavorable. According to recent newspaper report deaths have occurred after the use of large doses of this drug.—Eds.]

Perifolliculitis Capitis Abscedens et Suffodiens: Report of Case and Response to Therapy. According to Walter C. Gasner (Mount Vernon, N. Y.) the drugs of choice in treatment have been the sulfonamides, but results have not been too gratifying. A case is reported in which response to chloramphenicol was rapid.

Negro man, 34, had an eruption of 2 years' duration, limited to the scalp. There was a firm, sausage-shaped elevation toward the occipital area. Over the vertex were several areas of induration, two with small draining sinus tracts. The hair was absent in the involved areas. Treatment consisted of hot boric acid compresses for 1 hour daily, daily shampoos with liquid germicidal detergent and 1,000 mg chloramphenicol daily in divided doses. After 2 weeks, there was pronounced improvement and no active lesions. Chloramphenicol was reduced to 500 mg daily. The sausage-shaped lesion remained the same and alopecia in the healed areas was still present.

► [As with other deep-seated purulent infections, it is most important to persist in use of antibiotic therapy. In a similar case affecting a white woman, systemic broad-spectrum antibiotic, together with local hot compresses and a topical antibiotic rubbed in well several times daily, resulted in cure and hair regrowth. Therapy was continued for many months with gradual reduction of the dose of the systemic antibiotic and tapering off of the use of external measures.—Eds.]

Further Studies in Use of Gelatin in Treatment of Brittle Nails are reported by Saul Rosenberg, Kurt A. Oster (Bridgeport, Conn.), Andrew Kallos and William Burroughs[2] (New York). Patients were instructed to ingest 1 package (7 Gm.) of gelatin daily. A hole was drilled in the proximal edge of a nail and the nail was photographed. Most patients were seen twice a month and rephotographed. Of 50 patients in whom nail brittleness alone was manifested 43 (86%) showed improvement within 3 months. After treatment was stopped, brittleness of the nails recurred in many patients within 2-3 months but improvement was again observed when treatment was resumed. Blood calcium and phosphorus studies showed no etiologic relation to nail pathology. The BMR varied from +20% to −16%.

Of 12 patients with psoriasis of the nails who took gelatin

1 New York J. M. 57: 947-948, Mar. 1, 1957.
2 A.M.A. Arch. Dermat. 76: 330-335, September 1957.

lesions resistant to antibiotics particularly in 6 of scrofuloderma. Combined treatment of this type should be reserved for patients who do not respond to antibiotics and vitamins, since it presents the risk of increasing tuberculosis. For this reason it is contraindicated for routine use. A study of the isoniazid metabolism in 250 blood examinations showed an increase in isoniazid levels after addition of cortisone thus confirming the potentiating effect of the latter

The histologic study of lesions during antibiotic treatment showed changes previously described by Vandermeiren and Achten which proceed to collagen sclerosis an end stage common to all healing processes

The advantage of a combination of specific antibiotic therapy with nonspecific treatment affecting the general and local state is stressed with particular reference to the successful results obtained with specific antibiotics and vitamin D_2.

Clinical Aspects of Treatment of Some Dermatoses with Isopropyl Derivative of Isoniazid Preliminary Report. In treating 31 patients with various dermatoses Antonio Sapuppo[9] (Univ of Catania) used Marsilid® the isopropyl derivative of isoniazid in daily oral doses of 3-5 mg/kg body weight for an average of 30 days

One patient with ulcerative tuberculous lupus recovered and 1 with the closed type of tuberculous lupus showed improvement Patients with erythema induratum erythema nodosum papulonecrotic tuberculids and lupus erythematosus were benefited The best results were seen in those with psoriasis in whom the scales became dry and easy to remove the erythema diminished and the smaller lesions healed. In the larger lesions the healing process began at the center and progressed toward the periphery assuming the aspect of a margin covered by easily removable scales enclosing areas of healthy skin Biopsy of the center areas showed normal epidermis. The improvement continued even after discontinuing therapy

Side effects, such as constipation insomnia, difficult urination lowered sexual impulses and vertigo were never severe enough to necessitate discontinuance of the treatment and the patients appetite increased resulting in notable weight gains (6 kg in 1 month in 1 patient)

The mode of action of this derivative is not clear A gen

(9) Minerva dermat. 31 331-342. October 1956.

eral hypotension with orthostatic values lower than the clinostatic values seen in some of the patients suggested that besides its chemotherapeutic action the drug may have a pharmacologic action on the peripheral vessels

► [Our own experience with Marsilid® in the treatment of psoriasis has been unfavorable. According to recent newspaper reports deaths have occurred after the use of large doses of this drug.—Eds.]

Perifolliculitis Capitis Abscedens et Suffodiens Report of Case and Response to Therapy According to Walter G Gasner[1] (Mount Vernon N Y) the drugs of choice in treatment have been the sulfonamides but results have not been too gratifying A case is reported in which response to chloramphenicol was rapid.

Negro man, 34, had an eruption of 2 years duration, limited to the scalp There was a firm, sausage-shaped elevation toward the occipital area. Over the vertex were several areas of induration, two with small, draining sinus tracts The hair was absent in the involved areas. Treatment consisted of hot boric acid compresses for 1 hour daily daily shampoos with liquid germicidal detergent and 1 000 mg chloramphenicol daily in divided doses. After 2 weeks, there was pronounced improvement and no active lesions. Chloramphenicol was reduced to 500 mg daily The sausage-shaped lesion remained the same and alopecia in the healed areas was still present.

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(9) Minerva dermat. 31 331 342. October 1956.

tient became confused, underwent persistent tonic seizures and died.

CASE 2.—Man, 51, had acute monocytic leukemia of the Naegeli type with extensive leukemia cutis. Demecolcin was given in doses of 5 mg. daily for 5 days, resulting in a rapid decrease in the total leukocyte count (from 67,000 to 5,900), but no change in the systemic condition of the patient. The skin nodules showed a rapid resolution, but severe phthora stomatitis developed and the patient died after 20 days of hospitalization.

► [The search for effective chemotherapeutic agents for systemic malignant diseases, unfortunately, has thus far been without much success. Drugs of this group, which inhibit cell mitosis in the metaphase, might be used to advantage in combination with other agents, such as various forms of ionizing radiation.—Eds.]

Evaluation of Various Antihistamines as Local Anesthetic Agents. Recently studies were made on the use of antihistamines as local anesthetic agents. In general, the results were superior to those obtained with procaine. Toxic effects due to the local injection of antihistamines have been reported, however. These consist of erythema, necrosis and ulceration at the site of injection. Charles George Steffen, Richard Mihan and Murray Zimmerman (Univ. of Southern California) further evaluate the local anesthetic action and side effects of 4 antihistamines.

METHOD.—The antihistamines, 1% in isotonic saline, were made available in identical multiple dose bottles labeled A, B, C and D. The agents used were tripelennamine (Pyribenzamine®), pyrilamine maleate (Neo-Antergan®), diphenhydramine hydrochloride (Benadryl®) and chloroprophenpyridamine maleate (Chlor-Trimeton®). The surgeon was given an unlabeled, filled syringe and the operation was performed in the usual manner. After each surgical procedure, the bottle label, type of procedure and amount of drug used was noted by an independent observer. The surgeon noted whether the drug produced satisfactory anesthesia. The surgical procedures consisted of scalpel biopsies, electrodesiccations and curettements, small skin grafts and excisions of tumors.

✓ Benadryl was a satisfactory anesthetic agent in 14 of 15 cases; Neo-Antergan in 13 of 15, Chlor-Trimeton in 1 of 15 and Pyribenzamine in all 15 cases. In no case was the surgeon forced to interrupt the procedure and use a different anesthetic. The anesthetic was considered unsatisfactory if the patient was having any discomfort. There were no delayed reactions and wound healing progressed normally in each patient. The amount of drug used varied from 0.5-5 cc.

The method of anesthetic action of the antihistamines is not known. It is not due to local edema produced by the injec-

(J. Invest. Dermat. 29:7 8, July, 1957)

5 improved No improvement was noted in 14 patients with onychomycosis

Histologic studies of brittle nails showed no qualitative differences between these nails and normal ones. However brittle nails laminated more during cutting than normal nails and psoriatic nails most of all In the normal nail, there is microscopic evidence that the body of the nail is composed of parallel rows of keratin arranged in layers. No definite evidence of a cement substance holding the layers together was found

► [*Although we have observed gratifying effects with gelatin in strengthening brittle nails in some of our patients, we have not had the high percentage of successful results reported by Rosenberg and co-workers.—Ed.*]

Treatment of Leukemia Cutis with Demecolcin. Demecolcin is an alkaloid of Colchicum autumnale Experimental evidence demonstrates that it inhibits mitosis in metaphase but its toxicity appears to be 30 times less than that of colchicine. Unlike other cytotoxic agents used in treating leukemia, its action on hemopoiesis is a unique selective inhibition of granulocyte production There has been some success with demecolcin in acute granulocytic leukemia and some suggestive benefit in Hodgkin's disease and other tumors Most authors agree that it may be harmful in lymphocytic leukemia however The best therapeutic results are seen in chronic granulocytic leukemia and are characterized by a striking improvement in general clinical condition rapid decrease in splenomegaly and a diminution in the total number of granulocytes The remissions are short lived if the drug is stopped, whereas a prolonged remission may be obtained by continued maintenance therapy The dosage of demecolcin is not well established but has averaged about 5 mg daily To date the toxic effects have been minor and usually subside after discontinuing the drug

Edward Shanbrom and Daniel Kahn[3] (V A Hosp West Haven Conn) report resolution of skin lesions in 2 patients

CASE 1—Man, 36, had chronic granulocytic leukemia and was extremely ill when demecolcin therapy was instituted After 3 days of therapy the total leukocyte count dropped from 250 000 to 30,000 The differential count was essentially the same and there was no decrease in the number of blast forms seen. The general condition of the patient improved temporarily with a dramatic regression of the nodular skin and mucous membrane lesion However hemorrhagic manifestations of epistaxis, purpura and melena increased, the pa

(3) Ann. Int. Med 47 565-574, September 1957

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(1) J. Invest. Dermat. 10:7-8, July 1957.

tion of the solution because saline produced no anesthesia when tried as a control injection

► [Although the need is rare, there is the occasion when some substitute for procaine and chemically related local anesthetics is very desirable. This "blind" evaluation of selected antihistaminics brings evidence that they may be used as local anesthetics for dermatologic surgical procedures. Our own experience with Benadryl® solution (10 mg./cc. solution, as packaged) for this purpose also has been satisfactory.—Eds.]

Some Effects of Topical Vitamin A on Human Epidermis. Leah Fisher and Franz Herrmann[5] (New York Univ Post Grad Med School and Skin and Cancer Unit) examined the effect of vitamin A on human skin by means of planimetric measurements on histologic serial sections. Four skin biopsies were made from each of 8 healthy persons aged 24-34 before and after inunction of about 9 000 units of vitamin A daily in skin areas 1 cm in diameter for 3-5 consecutive weeks In some areas vitamin A in sesame oil was used, whereas in others the vehicle was an emulsion base No increase in thickness of the epidermis was observed in the treated areas Planimetric measurements also failed to demonstrate any increase in thickness of the epidermis in 1 person whose skin was studied before and after oral ingestion of vitamin A palmitate 200 000 units daily for 1 month

Arsthinol (Balarsen®) in Dermatology Good results have been reported in treatment of yaws and amebiasis with arsthinol Leon Goldman Robert H Preston and Morris Meister[6] (Univ of Cincinnati) treated 127 patients with 100 mg the 1st day 100 mg twice daily the 2d day and 100 mg 3 times daily the 3d day If no untoward reaction occurred, 300 mg a day was continued for 7 more days

Side reactions occurred in more than 10% of the patients but subsided promptly when medication stopped Side effects included dermatitis in 9 instances including exfoliative dermatitis in 2 patients and a bullous eruption in 1 and there was associated stomatitis in 1 In 4 patients fever developed 2 had diarrhea 1 had albuminuria and hematuria and 1 was nauseated In an effort to reduce frequency of side reactions only 50 mg twice daily was given to several patients. There were no reactions with this dosage some patients received the drug for 1 month

Therapeutic results with arsthinol have been encouraging

(5) A.M.A. Arch. Dermat 75 667-670, May, 1957
(6) Dermatologica 113:369-374 December 1956.

in lichen planus of 45 patients treated, 32 improved. Of 10 patients with nummular dermatitis 6 improved. Improvement occurred in 6 of 21 patients with verrucae, in 3 of 4 with aphthous stomatitis in 2 of 5 with dermatitis herpetiformis, in 2 of 6 with psoriasis and in 2 of 5 with localized neurodermatitis. Therapeutic response was slower in patients receiving the reduced dosage.

► [Arsthinol is an organic, trivalent arsenical formed by reacting 2 acetamido-4-hydroxybenzene-arsonous acid with dimercaprol. Thus it is cyclic 3-hydroxypropylene ester of 3-acetamido-4-hydroxydithiobenzene. Incidence of 17 cases of drug eruptions, fever etc., among 127 patients with benign dermatoses treated, appears prohibitive especially in view of the moderate therapeutic efficacy.—Eds.]

Onchocerciasis Review of Five Cases Treated in Britain with Diethylcarbamazine is reported by A. Girdwood Fergusson and James C. P. Logan (Glasgow) Of the 5 patients, 4 the diagnosis although presumptive was highly probable. These patients were Europeans living and working within 30 miles of the home of the 5th patient, an African, in whom diagnosis was definite. Diagnosis may have to be made in absence of subcutaneous nodules which contain the adult nematode, and without showing microfilariae in the skin The only criteria may be a history of residence in an infested region, raised eosinophil count when other parasitic conditions have been excluded and nonspecific pruritic eruption that responds to diethylcarbamazine.

Rarity of nodules occurring in the white races has been reported by others. Nodules were not found in the 4 Europeans Lichenification was observed in 2 patients slight elephantiasis of the thigh in 1 and eosinophilia of 12% or more in 3 Clinical signs consisted mainly of erythematous papulosquamous and papulopruriginous eruptions on extensor surfaces of the extremities and on the trunk. Adenitis was present in 2 and urticarial lesions that were not accompanied by dermographism in 1

All 5 patients responded well to treatment with diethylcarbamazine and have remained well for 1-7 years. These results are in marked contrast to the unfavorable results recorded by other workers. It may be that the nematodes, whether adult or embryonic, are more accessible to diethylcarbamazine when not protected by the subcutaneous nodules

(7) Australian J Dermat 3 10, December 1 56.

Treatment of Trophic Ulcers of Soles of Feet in Leprosy with Certain Hydrogenated Ergot Alkaloids. A mixture known as CCK 179 (Hydergine) injected intra arterially is reported by B B Gokhale[8] (Poona India) Nineteen patients were treated with 0.3 mg Hydergine on alternate days or every third day In 9 *the ulcers did not recur* in 4 they recurred in 1 a fresh ulcer developed at a different site 5 could not be followed To heal the ulcer 1-80 injections were required

The good results obtained are due to improved blood supply although it is not known precisely what part impairment of blood supply plays in the etiology of trophic ulcers. Hydergine was used because it contains 3 ergot alkaloids which are synergistic in their effect This mixture is reported to promote dilatation of peripheral vessels by (1) a peripheral adrenosympatholytic action (2) a direct dilating action on the smooth muscles of the vessel walls and (3) an inhibitory action on a central vasomotor center with subsequent lowering of vasomotor tone and consequent diminution of arterial tension Oscillometric and arteriographic studies should be of value in future studies Presumably Hydergine *is worth a trial in the treatment of trophic ulcers in leprosy* and it may be possible to stabilize treatment by its use Other therapeutic measures including the local use of antibiotics, hyaluronidase and gelatin sponge powder in conjunction with surgical and orthopedic measures rest and postural treatment will no doubt improve the results

► [According to the authors, CCK 179 or Hydergine (Sandoz) contain equal amounts of the following hydrogenated ergot alkaloids (1) dihydroergocristine, (2) dihydroergocornine and (3) dihydroergokryptine —Eds]

Intoxication by Aminopterin Used as Abortifacient. F Munroe Bourne Samuel O Freedman and Guy E Joron[9] (*Montreal Gen'l Hosp*) report a case.

Woman, 44 took 10-17 mg (exact amount unknown) of aminopterin during 3 days. The next day she noticed puffiness and redness of the face, and sore throat By the next day there was fiery red, diffuse erythema of the entire face and anterior neck. The face was swollen and several small clear vesicles were present on the chin, cheeks and eyelids. The lips were cracked and peeling The gingivae were pale and covered in most areas by whitish exudate The buccal mucosae and soft palate were red, edematous and covered with large patches of grayish white exudate. Petechial hemorrhages were scat

(8) Dermatologica 113 142 155 1956
(9) Canad. M A J 76 473-475 Ma 15 1957

tered over all the mucous membranes. The pharynx was congested and mildly edematous. The patient could speak only in hoarse whispers and had severe pain on swallowing. There w blotchy pink macular eruption on the anterior chest, the abdomen and flexors of the arms. There were no digesti tract symptoms. Blood count wer normal. Urinalysis was negative.

Citrovorum factor 0.5 mg. was given twice daily. Penicillin and streptomycin also were given. Local therapy consisted of hydrogen peroxide mouthwashes, wet dressings of milk and water and hydrocortisone cream. The lesions on the face and in the mouth were unchanged for 3 day and then began to improve slowly. On the 6th day the patient had vaginal bleeding and lower abdominal pain. Exploration of the uterine cavity revealed a small amount of decidual tissue.

During the next 8 days, the skin and mouth lesions healed rapidly and the patient was discharged. On the day f discharge her hair came out in handfuls as she combed it. Two weeks later about 75% of the scalp ha had been lost, but 6 weeks later there w beginning regrowth.

The toxic effects of aminopterin are typical of fol c acid deficiency and consist chiefly of lesions of the digesti e tract and hemopoietic ystem. Two day to se eral months after toxi doses wh tish necrotic areas may appear on the hard and soft palate th uvula bu cal mucosa, gums or lips. The t mal lesions usually heal in 3-14 days. Intestinal lesions may precede or follow the stomal ones. Due to intestinal ul eration, bdominal cramps, diarrhea and bleeding may oc cur. I olvement of the hem poietic system leads to depres s f bon marrow activity and may be characterized by leukopenia thrombocytopenia and anemia. Clin cal features nclude petechiae, bleeding gums and fever. Other tox c ef fect ncl de sensitivity reactions in which macular rashes a feature. Alopecia may develop. Citrovorum factor s a pecific antidote.

* [Because of its action as an abortifacient, aminopterin in New York City must be dispensed by hospital or the prescribing physician. It is illegal for pharmacists to dispense it, even on prescription. On the dosage schedule for the treatment of psoriasis of 0.5 mg. once daily for 1 eek alternating ith rest period of 1 week, as suggested by Rees, repeated for as many as 7 such courses, we hav not seen any serious sequelae. Depression in hite blood cell count has been noted in only 1 patient and depression of the red blood cell and platelet count in another. These changes ere reversed promptly on withdra al of the drug.—Eds.]

Skin Biopsy Technic is described by Marcus R. Caro[1] (U. iv. of Illinois). A specimen obtained from an area chosen haphazardly removed inadequately or fixed or stained incorrectly may disclose no helpful information no matter how skilfully it may ha e been excised and may even lead to er

(1) A.M.A. Arch. Dermat. 76: 3 July 1957

roneous conclusions Therefore selection of the biopsy site is a critical step The lesion selected for removal should be fully developed and uncomplicated If several types of lesions are present a specimen should be obtained from each type to determine whether several dermatoses are present.

In many cases much can be gained by removing the biopsy specimen from the border of the lesion including a small area of normal tissue Presence of normal tissue at the side of the section makes possible study of the advancing border This is especially useful in tumors and chronic granulomas. Before such a specimen is removed it should be transected with superficial incision or an indelible linear marking that will cross the lesion and the normal border This directional marking will enable correct cutting of the specimen and insure that each section will contain pathologic and normal zones

For most lesions the preferable method for obtaining a suitable specimen is cold steel surgical removal In suspected basal cell epithelioma or seborrheic keratosis, sufficient material for diagnosis can generally be obtained by use of a small sharp curet Pedunculated lesions may be clipped off with scissors care should be taken to include the base of the lesion Small specimens may be removed with a cutaneous punch For a large deep biopsy an elliptic excision with scalpel should be performed and the wound closed with sutures For histopathologic examination of vesicles and bullae it is important to remove the entire lesion intact.

The specimen should not be removed from the skin with forceps or any other instrument that may squeeze it or in any way distort its original relationships It should be lifted up with a needle, curet or scalpel and if large enough to be curled the specimen should be flattened on a card before it is dropped into the fixative solution For routine sections the fixative used most often is 10% formalin When presence of mucin is suspected absolute alcohol should be used as a fixative

The specimen should be accompanied by all pertinent information about the case including the age and color of the patient and site of the biopsy A portrayal of the eruption with a gross description of the lesion and a listing of diseases considered in differential diagnosis will help the pathologist. In difficult cases such information may aid him in de-

ciding whether the histopathologic findings correspond to or conversely are incompatible with any of the dermatoses under consideration.

► [A biopsy taken by elliptic excision from the edge of the lesion and including some normal tissue has yet another advantage. The normal tissue can be used for the suture intended to approximate the wound edges, rather than the diseased tissue which often is too friable to hold this suture. In addition, the local anesthetic should be administered around the biopsy site when possible, instead of directly into it. This reduces the amount of extraneous fluid and edema in the tissue specimen to be examined microscopically.—Eds.]

Dermabrasion with Rasps: a simplified technic using forged steel sculpture tools having central handles and toothed working surfaces at the ends, is described by Douglas Torre[2] (Cornell Univ.). Routine operating room procedures and local anesthesia (2% aqueous procaine by injection) are used. Postoperative applications of 0.1% benzalkonium solutions and gauze dressings are used until crusts drop off 5-10 days after the procedure, which consists of manual abrasion of the involved areas to the desired depth by use of the rasps.

Advantages of dermabrasion with rasps over the sandpaper method are elimination of the risk of silicon granuloma, avoidance of clogging of the instrument, simplicity of instrument sterilization and ease of use. Advantages over the wire brush technic are simpler and cheaper equipment, a refrigerant is unnecessary, avoidance of grooving or cutting, sponges cannot be caught on a whirling brush, less skill and experience are required, an assistant is unnecessary and depth and margins of the abraded area can easily be evaluated. Disadvantages are slowness of the procedure and excessive amounts of local anesthetic may be required if large areas are to be treated.

Two patients were treated for rhinophyma and 24 for postacne scarring with the rasp technic, 1 by sandpaper and 8 by wire brush. Results varied from 20 to 75% improvement with little variation noted among the technics. Three patients showed pigmentation and 2 milia.

► [A conservative appraisal of yet another method for dermal abrasion. The use of the rasp seems to us like a worthwhile method for managing certain types of scarring and, as was suggested by Torre, also to treat individual remaining pits after abrasion done with the revolving wire brush. As the author states, this technic is safer than the sandpaper or revolving wire brush method. In the hands of the expert, however, the use of the revolving wire brush on frozen skin is faster and perhaps more effective. The

(2) A.M.A. Arch. Dermat. 74: [illegible]5-617, December 1956.

delay in bleeding which results from freezing the tissues with the Kurtin technic has the advantage of permitting one to see the field and depth of planing it would seem that this advantage is lost with local injection anesthesia.

The technic of planing frozen tissue with disk shaped revolving fraises attached to an angulated handpiece which is used by some dermatologists, also deserves much more extensive trial.—Eds.]

Surgical Treatment of Hyperhidrosis Types of Sweating Tests of Sweating Surgical Treatment Results. According to Geza de Takats[3] (Univ of Illinois) indications for surgical treatment exist when the patient's occupation or emotional status is such that the hyperhidrosis becomes a true handicap and pharmacologic measures do not control the disorder Excessive sweating may result from rise of external or body temperature, emotional stimuli or action of cholinergic and adrenergic stimulants There are a number of clinical conditions associated with excessive sweating Central cerebral lesions consisting of small foci in the anterior hypothalamus may release paroxysmal sweating phenomena. These foci may be due to encephalitis in childhood Sweating localized to a single extremity is of reflex nature usually associated with vasoconstriction Such lesions may be noted after deep thrombophlebitis in Buerger's disease or after nerve injury

Excessive sweating may interfere with the patient's work or prove embarrassing to people in the public eye whose handshake is significant It may result in bromhidrosis that cannot be masked by deodorants

Removal of the 2d and 3d lumbar sympathetic ganglions effectively dries the lower extremity below the knee The 1st lumbar ganglion is removed when the thigh needs to be denervated For the upper extremity the hand can be denervated by removal of the 2d and 3d sympathetic ganglions However removal of ganglions from the 2d to 5th dorsal levels is advocated when the axilla is involved in the hyperhidrosis

Excessive sweating of the trunk may result from denervation of all 4 extremities Therefore the 2 upper or the 2 lower extremities are sympathectomized depending on the patient's special need Should all 4 extremities need denervation this should be limited to the hands and the feet In patients operated on for hyperhidrosis the skin remains pliable and does not require special care Once a foot or leg has

(3) A.M.A. Arch. Dermat. 76 31 38 July 1957

become dry excessive sweating will not recur Regeneration of sympathetic fibers may occur in upper dorsal sympathectomy but if ganglions from the 1st to 5th dorsal level are removed, this is not a problem.

► [When excessive sweating is believed to be functional in origin, it would seem that psychiatric consultation should be sought before undergoing sympathectomy De Takats included an interview with psychiatric social service order for each patient scheduled for sympathectomy Although some needed psychiatric or psychoanalytic treatment, de Takats comments he has never seen hyperhidrosis (or hypertension) alleviated by such measures —Eds]

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2 ECZEMATOUS DERMATITIS ATOPIC DERMATITIS AND URTICARIA ALLERGY

Racial and Environmental Factors in Susceptibility to Rhus were investigated by Ervin Epstein and Earl R. Claiborn (Highland-Alameda County Hosp., Oakland, Calif) Charts of 12,000 private patients were reviewed, including 10,272 whites, 1,272 Negroes and 456 Orientals. Among the whites, incidence of rhus dermatitis was 3.2% among the Negroes 0.9% and in the Orientals no cases were seen. This was difficult to explain, since most professional gardeners in the San Francisco Bay area are Japanese.

Patch tests with rhus toxin were given to 899 persons. Positive reactions to 1 10 dilution were obtained in 20-35% of the whites, Negroes and Orientals born in the United States However among Orientals and Hawaiians born in their native countries only 1.3% showed positive reactions. A history of previous rhus dermatitis was given by 23% of whites 1?% of Negroes 17.8% of Hawaiians 5.5% of Chinese 12 ?% of Japanese and 12.7% of Filipinos However of those Orientals born in the United States the incidence was about 19% (the same as Negroes and whites) but among those born overseas, only 1 (0.17%) gave a positive history

Among the persons in the above group who thought that they had been exposed to poison oak or poison ivy 43% of those born in this country had been affected, whereas only 3% of those born overseas had had an attack of rhus dermatitis These findings indicate a hyposensitization in the group

) M A Arch Dermat 75 9 381, February 1957

born overseas. It is suggested that the mango of Hawaii and the lacquer plants of the Orient are more potent immunizers than the domestic plants These plants which belong to the rhus family are as common in the Hawaiian Islands and the Orient as poison oak poison ivy and poison sumac are in the States If further studies confirm these findings, extracts of mango and lacquer may be used to produce immunity to poison oak or poison ivy despite the failure of extracts of the local plants to do so regularly

► [Definite conclusions cannot be drawn from these studies until certain additional control data are available. If supported by these, the results are of the greatest possible theoretical and practical significance. What produces the lesser degree of sensitivity to rhus allergens in persons born in the Far East? Is it exposure to highly potent rhus allergens during childhood, as suggested by Epstein and Claiborne? Or is it exposure to rhus allergens in utero, e.g via mango fruit ingested by the mother during pregnancy? Experiments have shown that, at least in some species of laboratory animals, exposure to certain allergens during fetal life or during the first few days of life engenders tolerance to the allergen or diminished susceptibility to become sensitized to it.—Eds.]

Transfer of Allergic Contact Type Delayed Sensitivity in Man was accomplished by William L. Epstein and Albert M Kligman[5] (Univ of Pennsylvania) in a significant number of cases Successful transfer depends on a number of mutually interacting variables namely the sensitivity of the donor the number of cells transferred the nature of the allergen and the recipient.

The donor must be extremely sensitive. Few patients with naturally acquired contact sensitivity meet this qualification. Large quantities of leukocytes are required. Doubtlessly the chief reason for frequent past failures is that far too few cells were used. Material for transfer was obtained by one of three methods (1) from bullae produced by patch testing a sensitive subject with the specific allergen (2) from bullae produced by cantharidin and (3) from peripheral blood.

The nature of the allergen was extremely important in successful transfers Sensitivity to pentadecyl catechol one of the allergens in dermatitis producing plants of the genus Rhus, was much easier to transfer than sensitivity to 2 4-dinitrochlorobenzene or paranitrosodimethylaniline. An important consideration in attempting to explain this is the fact that nearly everyone has been exposed to rhus allergens and thus may in some manner prepare the soil Perhaps a past sensitivity has become latent and the injection recalls

(5) J Invest. Dermat. 28:291-304 April, 1957

t to a clinically recognizable state. An alternate possibility is that the prior exposure merely altered the subject s immunologic potential without actually sensitizing him.

The fourth important variable is the individual response of the recipient. Leukocyte injections from the same donor evoked quite variable responses in different recipients but leukocyte injections from different donors into the same recipient induced a pattern of reaction which was characteristic for that recipient.

In interpreting the problems of delayed sensitivity whether of the tuberculin or the contact type the pitfall of reasoning by analogy with conventional circulating serum antibodies, such as precipitins, agglutinins etc., provoked by bacterial and other antigens, should be avoided. A great deal is known about these latter antibodies, but it is clear that delayed hypersensitivity antibodies are of a quite different nature. Conventional antibodies are located principally in the gamma globulin fraction of serum but allergic contact dermatitis can de elop in patients with agammaglobulinemia. Although lymphocytes figure heavily in transfer studies of delayed sensitivity their precise role in delayed antibody synthesis has not been worked out, and it may be that they are not even the main source of ant bodies. Possibly the real role of the lymphocyte in delayed hypersensitivity is to act as the veh le by which centrally produced antibodies are distributed to the skin, accounting for the generalization of the sensitization after a local cutaneous antigenic stimulus. The skin itself does not make these antibodies nor does it contain sufficiently large mounts to transfer the sensitivity passively

► [For many years, ever since the work in laboratory animals by Landsteiner and Chase, it had been hoped that passive transfer of allergic contact sensitivity by means of white cell suspensions could be achieved. Epstein and Kligman appear to have succeeded in man where Haxthausen and the senior editor and his collaborators have failed.

However the report of Epstein and Kligman leaves many unexplained points. Among them are the following

1 The authors feel that they have succeeded, where others failed, because they transferred much larger numbers of cells. On the other hand, the authors themselves report successful passive transfer by means of cell-free or almost cell-free blister fluid.

The sensitivity which was supposedly passively acquired lasted a long time. The editors are of the opinion that this indicates either an active sensitization or combined passive and subsequent active sensitization in the recipients of the cells of the type previously discussed by Sulzberger and the senior editor

3. The marked differences in transferability of allergic hypersensitivity to different allergens is striking.

4 There is no adequate explanation for the failure to transfer sensitivity to pentadecyl catechol passively to 5 of 6 children.—Eds.]

Spread of Nickel Dermatitis was studied by Poul V Marcussen[6] (Copenhagen) in 552 women and 70 men. A difference in contact pattern apparently accounts for the preponderance of nickel dermatitis in women Men tend to acquire nickel dermatitis through occupational exposure whereas women become sensitized to nickel in jewelry and clothing (clasps fasteners zippers etc.) Spread or multiple sensitization occurred in 79.7% of the patients and seemed in general to be independent of predisposition infection previous eczematous lesions secondary allergic reactions and other factors which are often supposed to play an important part in spread of dermatitis Spread seemed to proceed in two ways (1) Spread to neighboring sites, including spread from the hands to the face and feet especially in men employed as nickel platers apparently was due in part to contamination with nickel particles. (2) Spread to the arms particularly the cubital flexures seemed to be independent of the primary eruption but dependent on degree of sensitivity and duration of the eruption This type is apparently similar to the autosensitization reaction observed in patients with hypostatic eczema

► [Marcussen is justified in concluding that it would be difficult to explain the frequent involvement of the flexor aspects of the arms on the basis of contamination with nickel particles However no satisfactory alternate explanation is as yet available. The so-called autosensitization reaction in patients with hypostatic eczema does not usually involve the antecubital spaces.—Eds.]

Contact Dermatitis from Neomycin Due to Dermal Delayed (Tuberculin Type) Sensitivity Report of 10 Cases. Stephan Epstein[7] (Marshfield Wis Clinic) showed that these patients were allergic to neomycin but that patch tests were often negative Proof of sensitivity was made by intradermal tests with 0 05 cc 1 1000 or 1 100 solutions of neomycin which produced papular reactions in 48 hours Histologic sections of these areas showed both epidermitis and dermitis.

Misleading observations tending to exclude neomycin as the causative factor were (1) resemblance of the neomycin dermatitis to an apparent aggravation of the pre-existing dermatitis, (2) improvement after use of ointments containing

(6) Dermatologica 115 596 607 October 1957
(7) Ibid 113 191 201 October 1956

comycin and hydrocortisone and (3) negative patch tests with neomycin

Observations confirming the causative role of neomycin were (1) preparations containing neomycin aggravated the dermatitis, (2) elimination of neomycin promoted reco ery and (3) intradermal tests with neomycin were always posit e, occurring in all 10 patients of this series. Control injec tions of 0.05 cc. neomycin of 1 1000 and 1 100 dilutions in 44 persons produced negati e reactions.

Presumably neomycin ointments can produce contact der matitis when patch tests are negative because there is probably more absorption by the diseased skin than by normal kin There may also be increased local sensitivity Remem bering the above pitfalls in diagnosis t is suggested that intradermal tests with the drug be done if contact derma titis is suspected and f the patch tests are negat ve.

► [Since Ludwig and the senior editor reported the first case of allergic sensitivity to neomycin in 1952 there has been steady increase in the number of similar cases. Epstein finding of dermal delayed type sensitiv ity ithout patch test sensitivity in some cases could ell has great prac tical significance

He gives a random list of 24 topical preparations containing neomy cin, and there are undoubtedly more It is important that the practitioner know the various medicaments which contain neomycin so that he is on the alert for instances of possible allergic sensitization to this antibiotic

At the meeting of the Society for Investigative Dermatology in June 1957 as pointed out that allergic contact dermatitis produced by neomycin is usually slow to develop, slow to spread and is often dry and scaly rather than vesicular and wet. This may be another reason hy the diag nosis is missed in some instances However there are also typical vesic ular eczematous eruptions due to neomycin.

The observation of delayed dermal sensitivity to neomycin in the absence of patch test sensitivity once more demonstrates that one is not justified in considering eczematous and tuberculin type sensitivity as being identical although they are similar in some of their immunologic features.

Pirila and Wallenius (Hautarzt 8 518, 1957) within 20 months sa 28 cases ith sensitization after use of neomycin-bacitracin ointment All of 25 patients patch tested reacted to neomycin and 18 to bacitracin. The authors consider the possibility of common component in the t o anti-biotics hich may explain these reactions —Eds.]

Allergic Sensitization to Adhesive Tape Experimental Study with Hypoallergenic Adhesive Tape. Any allergic reaction, as benign nd transient as it may appear to be, n ol es the risk that the patient who has acquired the capacity to react to one substance may have become sensitive to chem ically related substances also W th adhesive tape resins and turpentine most often cause allergic sensitization, followed

by rubber the other ingredients are sensitizers only in exceptional cases The following cross-sensitizations may result from allergic sensitization to adhesive tape. (1) *Sensitization to natural rubber* may bring about cross sensitization to monomeric isoprene gutta percha and products containing acyclic terpenes such as lavender geranium vervein, saffron carrot tomato citrus peels and cod liver oil. (2) Sensitization to turpentine may result in allergic reactions to many products containing this substance which are widely used in everyday life. (3) Sensitization to resins in adhesive tape may bring about sensitization to various terpenic resins used in other materials such as varnishes

Edwin Sidi and Marc Hincky[8] (Paris) studied a new hypoallergenic adhesive tape containing 800 parts vinylic butyraldehyde, 1,200 styrene isobutylene copolymer 1 050 butyl phthalate and 200 zinc oxide One of the advantages of this formula is the small number of substances used which further reduces probability of causing an allergic reaction The tape does not have the same adhesiveness as conventional tapes at room temperature and as adhesiveness is increased by warming it should be pressed to the skin for a few moments when it is applied When this tape was used in patients patch tested for contact allergens reactions to tape were markedly reduced. Of 2 107 patients 77 showed allergic reactions to ordinary tape and only 18 to the hypoallergenic tape Of 37 suspected of being sensitive to rubber 17 reacted to ordinary adhesive tape and 4 to the new tape.

Although the precautions which have to be taken to insure adequate adhesiveness present some inconvenience the hypoallergenic tape has been useful in treatment of circulatory disturbances of the lower leg and certain torpid ulcers in patients allergic to ordinary adhesive tape

► [This hypoallergenic adhesive tape (Albuplast) and patches made with this tape (Neodermotest) are made in France by Jean Huerre & Co. —Eds.]

Detailed Analysis of 1 000 Patients with Contact Dermatitis *Hospitalized at Bulovka Hospital, Prague between 1953* and 1955 is reported by Anna Voldánova[9] (Postgrad. Med School Prague) The lesions were present for the first time in 52.9% They recurred twice in 13.7% 3-10 times in 9.3%

(8) J vest. Dermat. 29:81 90, August, 1957
(9) Československá dermat 32 60 71 1957

and more often in 17% Duration of hospitalization was 4-96 days (average 16 8) and ambulatory treatment lasted 1 day to 7 years. Highest incidence (17.9%) was observed in salaried patients, in whom dermatitis was usually caused by topical medicaments followed by workers in automobile, paint and heavy industry (17.7%) and domestic helpers (14.6%) Lowest incidence was found in miners (1 1%) hair dressers (0.9%) and shoe makers (0.5%)

The cause was suspected from history in 70.6% and confirmed by patch tests in 27 4% Routine tests gave positive reactions to substances to which the patients were known to have been exposed, in an additional 14.7% In the others the cause remained undetermined but 37.9% of these patients were not tested. Sensitivity to various materials handled at work was found in 17.3% and to working clothes and shoes in another 0.6% Cosmetics gave a positive reaction in 3.5% floor and furniture waxes in 3% rubber in 2.8% chemicals used in dry cleaning and dyeing of fabrics in 0.5% flowers in 0.4% and leather in 0 3% Drugs commonly used in dermatology caused dermatitis in 9.6% hemorrhoidal preparations in 2.4% ointment base in 0.7% and first aid bands in 0 8%

Routine skin tests were performed in 512 patients with eczema. The substances commonly used that gave positive reactions were turpentine (184) sodium hydroxide (79) mercuric chloride (74) Peruvian balsam (73) hydrargum precipitatum album (68) sulfathiazole (60) various soaps (41-61) procaine (59) salicylic acid (58) methyl alcohol (58) anilin (57) chrysarobin (55) formaldehyde (50) benzoic acid (43) resorcinol (37) boric acid (28) benzene (7) The severest reactions occurred with turpentine, procaine benzene and resorcinol. High frequency of positive reactions t substances often used in therapy suggests that preliminary sensitivity tests should be done as routine procedure.

► [There may be many points of difference between East and West, but the incidence of contact dermatitis due to topical medicaments is high on both sides of the iron curtain

The author apparently is not referring to allergic contact dermatitis alone in this study The high incidence of positive patch-test responses to chemicals such as sodium hydroxide, various soaps, methyl alcohol and others as well, which in our experience do not cause sensitization or are infrequent allergenic sensitizers, leads us to believe that primary irritant reactions have been included among the positive patch-test reactions. —Eds.]

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(8) J. Invest. Dermat. 29:81-90, August, 1957
(9) Ceskoslov. dermat. 32:60-71, 1957

and confirmed by testing In another bullous dermatitis was probably due to eucerin and in a third, dermatitis of the hands was probably caused by eucerin. In the other 7 eucerin could not be established as the certain cause of the cutaneous manifestations.

Positive eucerin tests were considered to be stigmas of previous sensitization because 7 patients with positive tests had had dermatoses of long standing e.g. ulcus cruris for 36, 17 and 2 years or chronic dermatitis of the hands for 37, 17, 9 and 4 years, and most likely had been treated with eucerin containing ointments. Two patients showed positive tests with other ointment bases, e.g. the ointment bases of chlortetracycline and suprathricin ointment, which probably contain lanolin alcohols and hog lard. One of these 2 patients had urticaria that was confirmed by anamnestic data and positive intracutaneous tests to be caused by hog lard. None of the patients reacted to wool fat, petrolatum or paraffin.

In 9 patients, a polyvalent sensitization had been assumed apparently erroneously because epicutaneous tests had been carried out with test substances dissolved in eucerin. Detailed testing with the constituents of eucerin, i.e. with eucerit (lanolin alcohol mixture), mineral oil (the solvent for eucerit), petrolatum and cholesterol (contained in amounts of 30-35% in eucerin) revealed lanolin alcohols to be the cause of positive epicutaneous tests in these 9 patients. The same group of substances is the cause of hypersensitivity to lanolin.

► [It is possible that the higher incidence of positive reactions in women is the result of their having much more opportunity for exposure to lanolin in creams and other cosmetics. Eucerin is the same or essentially the same preparation as Aquaphor and Nivea in the United States. Several previous studies have shown that sensitization to lanolin, lanolin alcohols, etc. is not at all rare. As a matter of fact, in a highly selected group of patients at the Skin and Cancer Unit, 4.4% were found to be sensitive on patch testing with lanolin.

Among the presently used ointment bases, it is our impression that carbowax bases and lanolin have the highest sensitizing potentials.—Eds.]

Cutaneous Chromoreactivity and Occupational Dermatoses: Clinical and Experimental Research is reported by Giuseppe Zina[3] (Univ. of Turin). A skin reaction to potassium dichromate can be considered proof of a specific allergic sensitivity. Patch tests with 0.5% potassium dichromate, 10% nickel sulfate, 5% cobalt sulfate, 10% terebenthine,

(3) Minerva dermat. 31:303-318, October 1956.

Contact Dermatitis Due to Hydrocortisone Ointment Report of Case of Sensitivity to Emulsifying Agents in Hydrophilic Ointment Base is presented by Wiley M Sams and J Graham Smith Jr [1] (Univ of Miami)

Woman, 49 had vesicular dermatitis on the foot after using a 1% hydrocortisone ointment (1% Cort Dome Creme) Patch tests with the ointment were *positive. Several months later the same ointment* was inadvertently prescribed for treatment of dermatitis on a finger A severe eczematous eruption appeared on the hands, forearms, face and neck. Patch tests performed with the ingredients of the ointment base were negative with beeswax, glycerin, liquid petrolatum and white petrolatum. Full strength applications of spermaceti and methylparaben gave questionable reactions. Patch tests with the self emulsifying wax (Ceramol) in the ointment and with sodium lauryl alcohol were positive but neither ingredient gave as severe a reaction *as that obtained from the base itself which contained both substances.*

The self-emulsifying wax is a partially sulfated fatty alcohol mixture in the 12-carbon atom to 18-carbon atom range sodium lauryl sulfate is a 12-carbon atom sulfated lauryl alcohol Both these substances especially sodium lauryl sulfate are widely used in ointment bases cosmetics, detergents and other preparations that come into contact with the skin Information concerning the ingredients of preparations for topical use should be more readily available so that the clinician may be better able to explain untoward reactions, to avoid irritation from certain materials and to select with greater skill the medicament to be used.

► [No case of allergic contact hypersensitivity to hydrocortisone itself has yet been reported. We strongly support the authors suggestion that "information concerning the ingredient of preparation for topical use should be more readily available

This article points out the importance of knowing the exact ingredients of everything that goes to ointments and other preparations for external use. It has been our experience that a letter of inquiry regarding the contents of topical medicaments addressed to the older well-established and reputable concerns often brings favorable response and at times even the offer to supply small quantities of each ingredient for testing purposes. —Eds.]

Observations and Investigations on Rare Hypersensitivity to Eucerin are presented by H J Bandmann and M Reichenberger [2] (Univ of Munich) Allergy to eucerin is rare It was found in 10 of 4 000 patients with dermatitis who were tested (about 0.25%) Thorough study of these 10 seemed to indicate that females showed a higher incidence (8 of 10) In 1 patient eucerin dermatitis was ascertained by history

(1) J.A.M.A. 164 1212-1213 July 13, 1957
(2) Hautarzt 8 11 13 January 1957

and confirmed by testing In another bullous dermatitis was probably due to eucerin and in a third dermatitis of the hands was probably caused by eucerin In the other 7 eucerin could not be established as the certain cause of the cutaneous manifestations.

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( ) Minerva dermat. 3 [illegible] [illegible] 1956.

2.5% formalin and 2% p phenylenediamine were made on 580 persons with dermatoses (very likely contact dermatoses) *in 70%* of whom one or more specific reactions were elicited Patch tests with 0.5% potassium dichromate were made on 139 construction workers with dermatoses. The reaction was negative or insufficient in 33 in 14 of whom the dermatosis was not occupational uncertain in 5 and strongly positive in 101

A constant negative reaction to this patch test in brick layers with diathetic eczema or allergic dermoepidermitis, due to topical medication with intensive allergies to the chemical compounds of the para group and the uncommon *presence of a generic polyreactivity in chromate-sensitive* persons are valid proof of the biologic specificity of the test. Only 5 chromate sensitive persons reacted positively to a patch test with 15% terebenthine and 3 of the 5 had had repeated contact with the substance

Analytic studies of Italian cements and intradermal and iontophoretic tests with water extracts of cement on 16 chromate-sensitive persons disclosed the presence of chromate salts in the cements Even in leather dermatitis chromate can at times assume the role of specific allergen

Of 17 patients with eczema who came into contact with both chromate and nickel on the job 2 were sensitive to nickel 2 to chromate 2 to both chromate and nickel and 2 to chromate and cobalt Of 139 chromate-sensitive persons, 28 reacted positively to a patch test with cobalt. As the intradermal and iontophoretic tests gave contradictory results evaluation of the nature and origin of skin reaction to cobalt salts is not possible at present It is assumed that the mechanism of reaction to cobalt is not like that to chromate. The author believes that the basic conditioning factor in dermatoses of construction workers is a definite predisposition of the person to eczematous reaction and that occupational contact is merely a concurrent cause or specific allergic stimulus.

► [The question arises whether the coexistence of sensitivity to chrome and cobalt and chrome and nickel is due to an immunologic relation between the two metals or whether it is an expression of the susceptibility of the patient to multiple specific allergic eczematous sensitization. The studies of Epstein (J Invest. Dermat. 25.269 1955) favor the latter possibility —Eds.]

Eczema of Hands Due to Triethanolamine in Cosmetic Hand Lotions for Housewives increased rapidly in the winter of 1955-56, according to Nils Thyresson Anders Lodin and Åke Nilzén Clinically the condition was characterized by nummular dry erythematosquamous areas of eczema on the dorsal aspects of the hands, wrists and finger bases. All patients showed positive epicutaneous reactions to one hand lotion and its triethanolamine content, but, with few exceptions, negative reactions to its other constituents (5 of 27 patients had positive reactions) Testing for sensitivity to various synthetic detergents and soaps produced no reactions.

Most patients had been using this hand lotion without cutaneous reaction for a number of years but for several years before the eruption occurred, they had used it after immersing the hands in new synthetic detergents. The sensitization is attributed to synergistic interaction between synthetic detergents and triethanolamine-containing hand lotions The ability of synthetic detergents to dissolve fats and reduce surface tension probably increases the penetration of the eczematogenic substance into the skin and facilitates sensitization.

► [The leading article of the 1956-57 YEAR BOOK pointed out the difficulties encountered in discovering the causative or contributing factors of certain cases of allergic contact dermatitis Thyresson and associates here present another example of the intricate series of events which may make for allergic sensitization, viz., the synergistic effect of household detergents and triethanolamine in producing allergic sensitization to triethanolamine While final proof for the correctness of this theory is still lacking, it is supported by the experimental findings of Nilzén and Wikstrom in laboratory animals (Acta dermat.-venereol. 35:292, 1955) —Eds]

Allergic Sensitization of Skin and Nails to Acrylic Plastic Nails is reported in 4 patients by Alexander A. Fisher Andrew Frank and Harold Glick[3] (New York Univ Post Grad. Med School and Skin and Cancer Unit) The self curing acrylic resins are created by polymerization of methyl methacrylate monomer and polymethyl methacrylate powder with an organic peroxide and an accelerator The liquid monomer has been proved to be the sensitizing agent, and the powder polymer is allergenically inert. All patients showed allergic eczematous contact reactions of the skin, onychial and paronychial tissues after application of the plastic nails (Fig 4) On patch testing all reacted strongly to the acrylic liquid monomer but not to the polymer which

(2) Acta dermat.-venereol. 36: 1[illegible], 1956
(3) J Allergy 28 84-88, January 1957

is consistent with previous findings on the use of monomer and polymer in dentures

In comparing the reactions to the use of acrylic plastic nails with those caused by phenol formaldehyde and synthetic rubber nail "undercoat it is noted that those of the former are more severe and of longer duration, that they may be accompanied by dermatitis of the fingers, face and eyelids and lead to permanent deformity of the nails involved which changes are usually not caused by the undercoat" *Pre use patch testing probably will not reveal allergic* sensitivity since this develops only after use of the material for 2-4 months

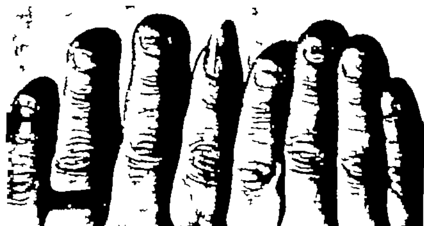


Fig 4 —Residual dystrophy 3 months after 1st and only application of acrylic nail plastic Both thumbnail (not shown) all nail of right hand and left 3d and 5th nails remained dystrophic Left 2d fingernail did not have any plastic applied Left 4th nail shows approximate condition of all nails before acrylic plastic applied. (Courtesy (Fisher A A et al J Allergy 28 84 88, January 1957)

► [A covering for the fingernail known as "Ten Day Nail has recently been introduced. It consists of a thin sheet of flexible plastic available in several colors with an adhesive on one side for application over the finger nail. Thus far we have seen no instances of allergic sensitization to Ten Day Nails, but we have heard others mention a few such cases and according to recent newspaper reports the Food and Drug Administration believes these "nails to be injurious.—Eds]

Patch Tests with Ether-Soluble Fractions of Mold Pellicles. Stephan Epstein (Marshfield Wis) Homer F Prince (Houston Tex) and Marie B Morrow[6] (Austin Tex) patch tested 135 patients with oleoresins prepared from various molds Many patients had contact dermatitis of unknown origin and contact with molds was considered a po

(6) J Allergy 28:313-315, July 1957

able cause. In 1 helminthosporium oleoresin repeatedly produced a positive patch test consisting of a tuberculin like reaction with erythema and swelling After 48 hours the lesions became follicular but never eczematous. The pa t ent had atopic dermatitis aggravated by house dust sensi ti ty and benefited greatly by desensitization with dust This appears to be the first case of a positive reaction to a mold oleoresin in man. The authors cannot correlate the re action with the fact that the patient had atopic rather than contact dermatitis, nor can they explain the tuberculin type rather than typical eczematous patch test reaction. The essentially negative results of this study do not exclude molds as a possible cause of contact dermatitis.

► [The question often has been asked whether mold oleoresins could produce allergic sensitization. Therefore, the fact that negative reactions occurred in the many cases of allergic contact dermatitis is of much interest. The "tuberculin type" response to patch test with helminthosporium oleoresin in the author's case of atopic dermatitis is impossible to interpret without additional data being available.—Eds.]

Conjunctivitis and Eyelid Eczema Due to Hypersensitiveness to Epinephrine Solution Employed in Spray Treatment of Asthma. H lge Colldahl and Erik Fagerberg (Stockholm) report case

Woman, 49 had intense conjuncti tis and redness, edema and itching of the eyelids for 5 months During this period, there had been repeated severe flare-ups followed by periods of relative quiescence. She had asthma and history of urticaria due to butter milk and medicine containing iodine Search for possible contact allergen as the ca se of the ey ymptoms w unsuccessful until spra solution (bectalin) which she used for asthma was suspected. Epicutaneous test w th the solution produced intense local eaction, with irritation and itching of the eyes When the bectalin was completely banned, the ey changes disappeared entirely within few days

Tests were made with the constituents of the spray chlorbutanol 0.5% natr pyrosulf 0.05% and epinephrine base 10% dissol ed in dilute HCl The epinephrine solution induced strong positi reac tion Control tests on other asthmatic patients were negative Tests ere made with epinephrine solution diluted 3, 10 and 100 times. The akest solution produced negati eaction, whereas the stronger ga positi reactions Epinephrine injections caused no symptoms other than local ischemia at the injection site, possibly because the solution is so much weaker than that used for inhalation.

► [Allergic hypersensitivity to epinephrine (Adrenalin®) has been reported from time to time, mor often in patients ho had received this substance prepared from suprarenal tissue rather than from synthetic material

Recently it as shown once more that the allergenic effects of certain

Acta allergol 1 77-81, 954

is consistent with previous findings on the use of monomer and polymer in dentures

In comparing the reactions to the use of acrylic plastic nails with those caused by phenol formaldehyde and synthetic rubber nail undercoat it is noted that those of the former are more severe and of longer duration that they may be accompanied by dermatitis of the fingers, face and eyelids and lead to permanent deformity of the nails involved which changes are usually not caused by the undercoat

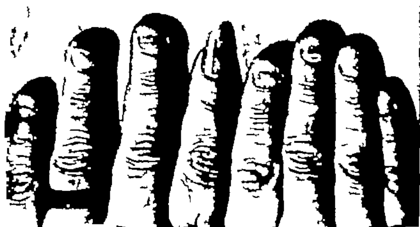


Fig 4 —Residual dystrophy 3 month after 1st and only application of acrylic nail plastic Both thumbnails (not shown) all nails of right hand and left 3d and 5th nails remained dystrophic Left 2d fingernail did not have any plastic applied Left 4th nail shows approximate condition of all nails before acrylic plastic was applied (Courtesy of Fisher A. A et al J Allergy 2[?] 84 88, January 1957)

Pre use patch testing probably will not reveal allergic sensitivity since this develops only after use of the material for 2-4 months

► [A covering for the fingernails known as "Ten Day Nail has recently been introduced. It consists of a thin sheet of flexible plastic available in several colors with an adhesive on one side for application over the finger nail. Thus far we have seen no instances of allergic sensitization to "Ten Day Nails, but we have heard others mention a few such cases and according to recent newspaper reports the Food and Drug Administration believes these nails to be injurious —Ed]

Patch Tests with Ether Soluble Fractions of Mold Pellicles. Stephan Epstein (Marshfield Wis) Homer L. Prince (Houston Tex) and Marie B Morrow[6] (Austin Tex) patch tested 135 patients with oleoresins prepared from various molds. Many patients had contact dermatitis of unknown origin and contact with molds was considered a po

(6) J Allergy 28 313-315 July 1957

area would be solely affected if the allergenic materials were disseminated hematogenously.—Eds.]

Primary Irritant and Allergic Eczematous Reactions Their Interrelations are discussed by Adolph Rostenberg Jr.[9] (Univ. of Illinois). An eczematous allergen is defined as a substance that is not primarily irritating on first exposure but which, in persons of appropriate genetic constitution, causes development of a delayed-type allergic sensitization, so that subsequent contact with concentrations that are nonirritating to unexposed or nonsensitized persons produces an eczematous reaction. A primary eczematous irritant is a substance that produces an eczematous response nonimmunologically. Many eczematous allergens are also primary irritants; some primary irritants are also eczematous sensitizers, but most are not.

The number of persons affected by a substance acting as a primary irritant is considerably more than the number affected by the same substance acting as an eczematous allergen, because of the different pathogenesis of the two reactions. For a primary irritant to produce a reaction, all that is required is that the substance be met in appropriate concentration, whereas for an allergen to produce an eczematous reaction necessitates that the allergen be met in suitable concentration and that the encounter be with a suitable person, i.e., a sensitized one. The lesions developed by primary irritants are roughly equivalent clinically and pathologically but there is far more variability than in those produced by eczematous allergens as there is a far greater range in intensity of response because of marked differences in the inherent irritant properties of different substances.

Although in development of an eczematous sensitization the intrinsic allergenicity and the genetic make-up of the host are the two main factors, there are also other influences. Certain fortuitous factors affect the host. These factors comprise a variety of influences, some of which are not precisely known while others are. One of these is concomitant inflammation, such as would be induced by a primary irritant. The influence of a primary irritant reaction on subsequent primary irritant reactions or on development of allergic eczematous reactions is of theoretical and practical importance.

Equally important is the possible influence of development

[9] A.M.A. Arch. Dermat. 75:547-558, April, 1957.

substances may well be due to accidental contaminants which one would not know about in the normal course of events. Brown and Coleman (J.A.M.A. 165:2178, Dec. 28, 1957) reported that vaccines filtered through silk filters caused severe allergic reaction in 3 patients who were discovered to be sensitive to silk.—Eds.]

Periorbital Dermatitis Following Adhesive Tape Strapping of Lower Extremities is reported by William A. Reyer[8] (Sharon, Pa.) in 4 patients who had been under the care of a chiropodist and had had corrective adhesive strapping for 6-12 weeks before the periorbital dermatitis appeared. 1 had varicosities of the lower extremities, 1 had stasis dermatitis and 2 had ulcers. All 4 were responding well to treatment by the chiropodist when the eruption appeared around the eyes. No local medication had been used in the 2 without ulcers. In the 2 with ulcers, penicillin ointment had been used, but neither showed evidence of sensitivity to the ointment, as ulcers and periorbital dermatitis healed with its continued use. There was no eczematous eruption under the adhesive tape.

All 4 patients showed long standing circulatory inadequacy of the feet and/or legs from foot strain or ulceration. The metabolism of musculature in spasm is different from that in relaxation, and when spastic muscles are relaxed by relief from pain through proper strapping, tissue protein metabolites may enter the circulation in pathogenic amounts. If an area of skin such as the eyelids has become sensitized to these metabolic elements over a period of months, dermatitis may develop when greatly increased amounts of the metabolites are suddenly present in the circulation.

Perhaps a combination of staphylococcus toxin with the tissue products may be the ultimate antigen. In 3 of the patients, a positive intradermal test was obtained with staphylococcus vaccine. This would be in accord with the findings of others that in autosensitization dermatitis, the antigen appears to be body tissue plus bacterial toxins.

► [In his paper, Reyer states, "The pathogenesis of this disorder can only be suggested in this paper, for such study is almost impossible in a busy private dermatologic practice." We agree that additional investigations concerning air-borne, contact and drug allergens, etc., as well as nonallergenic factors, are essential in these patients because doubt remains as to the correctness of the explanation given here for the cause of the eyelid dermatitis. The eyelids, to say the least, are uncommon sites for "id" reactions. This makes it difficult to accept the hypothesis that the periorbital

(8) Ann. Allergy 15:144-149, Mar.-Apr., 1957.

wa e liquids, hot wave solutions including sulfite preparations, thioglycolate and thioglycolate test preparations, cold wa e developers, and their chemical conversion products that had been stored for a long time and thioglycerin solutions

Primary irritation had not been found to occur with commercial cold wave developers (up to 10% thioglycolic acid, pH up to 9.5) Positi e results were seen only in hairdr ser persoon 1 with particularly intensive chronic cold wa e damage In 83 of 84 ha rdresser who mostly had been handling cold wa e preparation for at least 2 years no allergic reaction were found, although cold wa e damage was cl n ically obvious In such cases t might be rather the continual prolonged action of thioglycol developers that produces facultative irritant effects on the skin Sensitization by thioglycerin has practically been clarified and thioglycerin containing preparations are not now used. Tests with ether xtracted fractions f cold wa e solutions re ealed that emulsion and perf me parts were well tolerated whereas patch te ts with th thioglycolat part showed rr tation. Thioglycol cid patch tests (10% thioglycol c acid pH 4.0) were positive in 3 hairdressers who also howed posit e ammonium and monoethanolamine-thioglycolate tests, proof f an increased sensitivity not only to ammoniacal and monoethanolam e thioglycolate solutions but also to pure thiogly olic acid

M ld wa e liquids which conta n as the effecti e ubstance mmoniacal or monoethanolamine thiogly colat (like simple cold w e l qu ds) or in addition also ulfite (transition to hot wa e l quids) cause rritation in persons sensitive to old wa dev loper To analy e results of mild wave liquid testing pat h tests were also made w th hot wave liquid reaction wa positi e n 1 test person sensiti e to hot wave l quid only

It concluded that i person continually exposed to cold wa e preparations hypersen tivity to thioglycol cold wa e de lopers may occur although so far only sen itization to thioglycerin-containing developers had been proved.

II Experimental tests with chemical conversion products of old wave developer are the *object of a second report* by Bor lli[2] In cold wave developer produ tion, thioglycolic

(2) [illegible] 8 211 214, May 957

of an allergic eczematous reaction on subsequent allergic eczematous reactions or on development of primary irritant reactions. Certain persons with allergic eczematous sensitization to one substance as time goes on, acquire new eczematous sensitivities. This is known as broadening of the allergic base or polyvalence of the sensitization. Rostenberg does not deny that the acquisition of new "sensitivities" by the eczematously sensitive individual occasionally occurs but emphasizes that this is the exception. Clinical evidence and experimental studies support the view that persons with eczematous sensitization to a single substance maintain that single sensitivity for years and usually do not acquire new ones. Rostenberg believes that the polyvalence of the sensitization denotes increased nonspecific irritability of the skin rather than development of new allergic eczematous sensitizations, i.e., the eczematous person's threshold of tolerance for mild primary irritants has been lowered.

► [A clear review of the difference between substances which engender eczematous lesions on the basis of their inherent capacity to irritate and substances which cause such lesions on an immunologic basis.

The editors would differentiate sharply between two categories of multiple allergic eczematous sensitization:

(1) *A sensitivity to two or more allergens based on the principle of cross-sensitization*, i.e., on the immunochemical relation between two or more substances.

(2) Multiple specific sensitivities. As was first suggested by Rostenberg and Sulzberger, clinical experience shows that as a group, persons who have already developed an allergic eczematous sensitivity to two or more substances are more likely to develop additional allergic sensitivities than persons without previous sensitization.

These two categories must not be confused with nonallergic polyvalent sensitivity as seen, e.g., in patients with generalized spreading eczematous eruptions.—Eds.]

Toxic and Allergic Reactions to Organic Sulfur Compounds in Permanent Wave Preparations.—*I. Test studies with cold wave developers, hot wave preparations, base and related substances* are reported by Siegfried Borelli[1] (Univ. of Munich). Among a total of 970 patients, results were studied in 252: 157 of these were hairdresser personnel with marked, mostly chronic cold wave damage (75 hairdressers, 82 women attending hairdresser schools), 10 beauty parlor customers with dermatitis due to cold wave liquids, and 85 dermatologic control patients with sensitive skin or various skin diseases. Solutions used in epicutaneous patch tests included commercial cold wave developer, mild

(1) Hautarzt 8: 159-167, April, 1957.

liquid tests showed definite positive reactions to 0.25% solutions of distillation residues after 24 48 and even more hours disclosing a hypersensitivity to thioglycolic acid remnants contained in these residue solutions or to other distilled off chemical substances. The latter may also be present in less carefully manufactured cold wave developers.

[In order to understand fully the capacity of cosmetics and other substances which come in contact with the skin to produce local reactions, one must not only know the chemical ingredients but also be competent chemist or have available the advice of competent chemist. Only with such knowledge can one anticipate and look for various chemical reactions and their end products which may produce dermatitis.—Eds.]

Polyarteritis Cutanea Benigna is discussed on the basis of 8 pertinent cases by Pietro Cerutti and Giovanni Santojanni (Univ of Naples) Since periarteritis nodosa (panarteritis nodosa, polyarteritis) was described by Kussmaul and Maier its importance in dermatology has increased, particularly since it was found that polyarteritis belongs to the collagenous group may be generalized or localized and may occur in a few organs or in one organ, e.g the skin. Histologically vascular changes are of primary importance and show the characteristics of serous inflammation and fibrin d degeneration occurring ma ly in the media and adventitia Changes i th intima of smallest arterioles and capillaries also exist, and even veins may be involved. For these easons the terms periarteritis and panarteritis should be replaced by polyarteritis or polyvasculitis even the char cterization nodular should be relinquished si ce cutaneous nodules are often missing

Of the 8 cases reported, Cases 1 and 2 showed marked clin cal and structural milarities. In Case 1 nodular hypodermal, well-defined, pinki h to red-brown lesions were present in the upper third of the thighs for 5-7 months (F g 5) Structurally both cases revealed exudative proliferative hanges of walls of small hypodermal vessels and formation of proliferati e granulomatous tissue. In Cases 3 and 4 there wer nodular and deep subcutaneous platelike lesions and marked eosinophilia n the granulomatous tissue as well as in the blood (allergic granuloma) In Cases 5 and 6 infiltra t e nodular lesions of the lower extremities displayed a marked hemorrhagic character with degenerative and ul ceronecrotic changes subsequently developing in Case 6. Case 7 howed vascular changes of the panvasculitis type skin le

(4) Hautarzt 8 109 11, March, 957

acid (mostly 80%) is diluted to about 10% brought to pH 8.0-9.5 by alkalizing bases buffered and mixed with perfume solution glycerin sorbitol and water soluble polyglycols. Emulsion cold waves also contain lanolin or similar emulsion solutions These substances all of which proved negative in patch testing are added to alkaline ammoniacal or monoethanolamine thioglycolate solution, which is the effective substance and causes positive reactions. On the way from manufacturer to customer cold wave preparations may undergo changes e g insignificant amounts of iron from containers may cause minor reactions Hydrogen sulfide, which is not present in freshly prepared thioglycolic acid, forms after a few days particularly in strongly alkaline solutions and may cause dermatitis Because of oxidation dimerization may take place with formation of dithioglycolic acid ammonium dithioglycolates dithioglycolides and finally glycolid acid Dithiodiglycolic acid may also form in less carefully manufactured cold wave preparations. Besides a number of conversion products may arise which cannot be isolated. Most of these changes however produce alterations in color e.g., polysulfides cause a yellow color oxidation with small quantities of oxygen a yellow or black and with larger quantities of oxygen a reddish lilac. Most discolored cold wave liquids also have an unbearable smell.

Patch tests with discolored commercial cold wave preparations did not reveal toxic reactions. Positive results were seen only in test persons with damage to the skin due to cold wave developers i.e. those sensitive to cold wave liquids. Patch tests with solutions of conversion products and basic substances (ammoniacal thiodiglycolic acid dithiodiglycolic acid, glycolid acid and sodium alkaline glycolid acid) were negative (1 positive to doubtful in 178 tests) These chemical substances were rather well tolerated although some authors have considered them to be irritant even sensitizing agents. Patch tests with distillation residues of thioglycolic acid production revealed undiluted solutions of these substances to be primary irritants all control persons showed strong reactions although there was no necrosis or marked blistering and the reaction showed distinct involution or even had disappeared on the second day When concentrations of less than 2% were used no reaction occurred in controls. In the group of hairdressers 3 with positive cold wave

f equently reported associat on of polyarteritis with bron ch al asthma strongly favor a hyperreactivity fact r

In treatment, prednisone (Case 7) ACTH and cortisone w e ccessful and were preferable to antibiotics and vac ci es It is concluded that the designation polyarteritis hould include those cases in which only the skin is in olved (polyarteritis cutanea benigna) with a multiformity of clin ical manifestations.

Allergic Cutaneous Vasculitis Report of Unique Case in which the hief vascular abnormal ties were in the ubcutis presented by S Irgang[3] (Harlem Hosp., New York) The disorder s a polymorphous eruption primarily a macular erythema of the lower extremities in which the predom nant h tologi fi ding is arterioliti of the essels of the cutis.

Woman, 29 had painful tender swelling of the ankles and feet and an eruption on the lower extremities for 10 weeks. She had been treated for syphilis 8 months before Nonpruritic, pinkish red, discrete, spl t pea to bean-sized macules were symmetrically distributed over the thighs, legs and feet The central part of each lesion wa indurated. The blood VDRL wa 2+ Blood studies showed anemia, leukopenia, lymphocytosi and neutropenia. A microscopic section of the lesion revealed marked thickening of the arteriolar wall in the subcutis with perivascula infiltration by some lymphocytes and plasma cell There was also mild panniculitis. The patient received 15 daily intramuscular injections of 600,000 units of procaine penicillin ithout effect on the lesions. The eruption resol ed gradually and healing was complete about 6 months after onset.

Pathogenesis of th disease is believed to be related to hematogenou bacterial di semination. The ut tanding his t logic finding associated with other tissue variations, s se er a-cul t There is marked thicken g of the vessels all layers with evidence of degenerative changes Leukopenia and eutropenia indicate a general uppres ive action on polymorphonuclear leukocytes.

► [Proof that these eruptions are related to hematogenous bacterial dissemination and that they are based on an allergic mechanism is still lacking.—Ed.]

Basophil Leukocytes and Urticaria. Until recently l ttle ha been know bout the chemistry nd physiology of the basophil leukocytes Like the mast cell they probably contain hepari and there is ev dence they are the chief or sole carrier f histamine in the blood. Hans Rorsman (Un v of Lund) f und in 22 cases of urticaria a stat stically s gn fi cant decrease in the basophil leukocyte count a compared

(3) A.M.A. Arch. Dermat. 7 395-396, December 1 56.
( ) Acta dermat.-venereol. 37 2 (29

sions were polymorphic with predominant hemorrhagic and infiltrative necrotic traits Changes of the ocular fundus and coronary attacks probably indicated systemic involvement. In Case 8, in which at first the condition seemed to be panniculitis (Christian Weber) diffuse vasculitis of the granulomatous type existed at the dermal hypodermal border exudative and degenerative-necrotic changes were less marked.

Multiformity in clinical appearance is due to the variety of histologic changes all of which have in common vascular



Fig 5. (Courtesy of Ceratti, P and Santojanni, G Haútarzt 8 109-119, March 1937)

changes consisting of fibrinoid degeneration in the media followed by serous inflammation and simultaneous involvement of adventitia and intima Consequently tissue reactions include serous exudative change in the initial phase granulomatous proliferative changes of reticulohistiocytic or histiofibrocytic character in later stages possibly indicative of final cicatrization

In regard to etiology and pathogenesis of the polyarteritis syndrome, the authors stress the toxic infectious and allergic infectious origin Positive intradermal reactions to streptococcic vaccine (Cases 6 and 7) chronic tonsillitis with positive tonsillar test (Case 3) pyorrhea (Case 4) finding of marked tissue and blood eosinophilia (Cases 3 and 4) and a

XBF 6000) which has nearly the same effects as sunlight as far as UV and visible light are concerned and Kromayer lamp K 200 (Hanau) were used for testing sensitivity to UVB To single out spectral ranges of certain wavelength (particularly 3,130 A. and 2,699-3,025 A.) absorptions and interference filters (Schott) were used.

CASE 1.—Man, 41 in 1949 showed hypersensitivity to light. Since 1950 even after exposure to sunlight through windows, he had recurrences of erythematous, urticarial swellings. There was no reaction to cold, heat or pressure Prausnitz Küstner reaction was negative. Two minutes after 1½ seconds' exposure to a Hanau Hg lamp at 50 cm there was itching, erythema and whealing the erythema normally occurring within 9-24 seconds. Testing with various filters revealed the eliciting spectral range to be UVA, and possibly UVB and UVC.

CASE 2.—Woman, 43, had been hypersensitive to sunlight since 1953 Prausnitz Küstner reaction was positive. Erythema appeared 1½ minutes after 3 seconds' exposure t Hanau Hg lamp and ? minutes later there was urticarial swelling lasting about 10 minutes. Under Hg lines 2,699-3,130 A. an instantaneous urticarial reaction occurred. Further testing with filters showed the eliciting spectral range to include UV and the violet part of isible light.

CASE 3.—Man, 28, had first symptoms of light sensitivity with itching, erythema, urticarial swelling and malaise in 1953, relieved by 1 intravenous injection of calcium. The symptoms recurred in 1954 There were no urticarial reactions to other noxae, heat or artificial light Prausnitz Küstner reaction was positive. Erythema appeared 5-10 minutes after 4 seconds' exposure to Hanau Hg lamp (in males normally after 29-104 seconds) Under Hg lines 2,699-3,130 A. there was an immediate urticarial reaction. Testing with Xenon high pressur lamp and arious filters proved the eliciting spectral range to include UV and the violet part of visible light.

CASE 4.—Woman, 45 had had postprandial dyspepsia for 10 years. Urticaria occurred during pregnancy (22 years ago) and later after exposure to sunlight. Prausnitz Küstner reaction was positive. Exposure to the Hanau Hg lamp with average erythema threshold doses produced no immediate urticarial response. Under Kromayer lamp Hg lines 2,699-3,025 A and 1/5 and ½ erythema threshold doses, no reaction occurred under Hg line 3 130 A. and 1/5 erythema threshold doses, there was an erythematous reaction and under Hg line 3,655 A. wheal formation. Hypersensitivity to UVA and visible light but not to UVB and infra-red was, therefore, ascertained. Tests within isible spectral range with Xenon lamp and interference filters, however revealed 3 separated eliciting spectral ranges of 3,100-4,500 A., 4,900-5,200 A and 6,000-6,800 A

Th authors assumed Cases 1 3 to belong in the category f solar urticaria λ <3,700 A., especially since the Prausnitz K stner experiment was also positive. Case 4 however cannot be included either in solar urticaria type λ <3,700 A.

with the count in 96 normal controls. Average basophil count in urticaria was 8.1 ± 2.7/cu mm blood, whereas in controls the average was 44.8 ± 2.4 Only 1 patient with urticaria had a basophil count higher than the control average. Among controls there was only one count lower than the average for urticaria cases.

The number of determinations is too small to permit any conclusion as to frequency of lowered basophil counts in urticaria. It has not been possible to determine the importance of duration severity or cause of the urticaria on the basophil count Because of the histamine content of basophil leukocytes decrease in basophil count may be the morphologic counterpart of the blood histamine decrease in this disorder

► [Bernatu at the Skin and Cancer Unit has been able to confirm Rorsman's results. The fact that the basophil count in the blood of patients with urticaria is significantly lowered is an important new finding —Eds.]

Urticaria Associated with Giardiasis Lamblia. Rudolf E. Wilhelm[7] *(US Army Hosp., Fort Knox, Ky) reports* 2 cases. Urticarial episodes correlated well with presence of the parasite in the stool and treatment of the giardiasis was followed by disappearance of the urticaria. On return of the giardia in the stool urticaria also returned Fumagillin therapy resulted *only in temporary relief from urticaria* associated with temporary clearing of the stools but no recurrence of urticaria or giardiasis was observed after treatment with quinacrine hydrochloride

Cases of ascariasis oxyuriasis and tapeworm infestation *have been reported* associated with urticaria and eosinophilia, but the author's cases appear to be the first reported of urticaria associated with giardiasis lamblia. These cases suggest that this parasite should not be regarded as a normal nonpathogenic inhabitant of the human gastrointestinal *tract.*

► [It may come as a surprise to some that Atabrine® has been used successfully for about 20 years in treatment of intestinal giardiasis —Eds.]

Solar Urticaria and Its Eliciting Spectral Range. A. Wiskemann and K. Wulf[8] (Univ of Hamburg) describe 4 cases together with the method and equipment used for ascertaining the eliciting *spectral range.*

Exposure to global irradiation (sun plus sky generally spoken of as "sun) Osram Xenon high pressure lamp (type

(7) J. Allergy 28:351-353, July 1 57
(8) Arch. klin. u. exper Dermat. 203:394-408 1956.

XBF 6000) which has nearly the same effects as sunlight as far as UV and visible light are concerned and Kromayer lamp K 200 (Hanau) were used for testing sensitivity to UVB To single out spectral ranges of certain wavelength (particularly 3 130 A. and 2,699-3 025 A.) absorptions and interference filters (Schott) were used.

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CASE 2—Woman, 43, had been hypersensitive to sunlight since 1953 Prausnitz Küstner reaction was positive. Erythema appeared 1½ minutes after 3 seconds' exposure to a Hanau Hg lamp and 2 minutes later there was urticarial swelling lasting about 10 minutes. Under Hg lines 2,699-3,130 A. an instantaneous urticarial reaction occurred Further testing with filters showed the eliciting spectral range to include UV and the violet part of visible light.

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CASE 4.—Woman, 45 had had postprandial dyspepsia for 10 years. Urticaria occurred during pregnancy (22 years ago) and later after exposure to sunlight. Prausnitz Küstner reaction was positive. Exposure to the Hanau Hg lamp with average erythema threshold doses produced no immediate urticarial response. Under Kromayer lamp Hg lines 2,699-3,025 A. and 1/5 and ⅓ erythema threshold doses, no reaction occurred under Hg line 3 130 A. and 1/5 erythema threshold doses, there was an erythematous reaction and under Hg line 3,655 A. wheal formation. Hypersensitivity to UVA and visible light but not to UVB and infra-red was, therefore, ascertained. Tests within visible spectral range with Xenon lamp and interference filters, however revealed 3 separated eliciting spectral ranges of 3 100-4,500 A., 4,900-5,200 A and 6,000-6,800 A.

The authors assumed Cases 1 3 to belong in the category of solar urticaria $\lambda < 3{,}700$ A especially since the Prausnitz Kustner experiment was also positive. Case 4 however cannot be included either in solar urticaria type $\lambda < 3{,}700$ A.

(Blum Baer Sulzberger) or in type 4,000-5,000 A (Blum-Barksdale Green) This so far undescribed type of solar urticaria appears to be characterized by three different eliciting spectral ranges within UVA and visible light and also by the positive Prausnitz Kustner test.

Porphyrinuria was not observed but Kimmig's light band substances were found in the urine of all 4 patients. Light protective preparations were of little benefit in preventing this type of solar urticaria and the therapeutic effects of antihistamines should not be overestimated Calcium and cortisone therapy and the treatment of focal infections were of no benefit Desensitization by initially small, slowly increasing UV irradiation possibly combined with similar exposure to sunlight in spring are indicated

► [The abbreviations UVA UVB and UVC refer to the divisions of the ultraviolet spectrum of optic radiation as regards their biologic effects as follows UVA (400-315 mμ) with deep-reaching action, e.g., curative in lupus vulgaris, UVB (315-280 mμ) with erythema producing effect, and UVC (280 mμ) with germicidal effects (Wiskemann Hautarzt 7 16, 1956)

Case 4 is indeed unusual and does not appear to fit in with any other cases previously described It would be interesting to know whether this patient has one antibody which passively transfers sensitivity in all three spectral ranges or whether three separate antibodies mediate the sensitivities in the different spectral ranges.—Eds.]

Solar Dermatitis. According to John H Lamb Phyllis E. Jones (Oklahoma City) and Thomas B Maxwell[9] (Bakersfield Calif) clinical differentiation of plaquelike (the commonest type) polymorphic light eruption and discoid lupus erythematosus usually is not difficult The plaquelike eruption is pinkish shows slight follicular plugging clears without atrophy in winter affect the posterior cheek and mastoid areas by preference and is seen mostly in males (90%) Discoid lupus is purple red at the periphery and white and scaly in the center shows pronounced plugging heals with marked atrophy shows slight seasonal variation affects the butterfly areas of the nose cheeks and upper lip frequently and occurs mostly in females

The papular and prurigo-like type of polymorphic light eruption and the contact eczematous type present no problem in differentiation The multiforme type or erythema solare perstans may be confused with the evanescent erythematous variety of subacute lupus erythematosus In the erythema multiforme type of solar dermatitis the lesions are

(9) A.M.A. Arch. Dermat 75 171 180 February 1957

lighter and unilateral or worse on the left cheek (owing to exposure from the driver seat of motor vehicles) The general condition is excellent laboratory examinations are negative except for low sperm counts in the male and the condition is commoner in males In the erythematous type of subacute lupus erythematosus there may be joint pains low grade fever general debilitation and weakness. Laboratory examination may show a high sedimentation rate leukopenia, secondary anemia, reversal of the albumin-globulin ratio and presence of the L.E. cell The condition is commoner in females.

Microscopic differentiation between discoid lupus erythematosus and polymorphic light-sensitive lesions is difficult. After study of 30 polymorphic light-sensitive cases and 11 cases of lupus erythematosus several points of differentiation were evolved. Relative hyperkeratosis was common to both types of eruption but parakeratosis occurring with hyperkeratosis was seen only in light-sensitive disease (70%) Liquefaction degeneration of the basal cell layer was constant in lupus but was seen in only 40% of light-sensitive eruptions Acanthosis alternating with atrophy was seen in both types of eruption but acanthosis was a more pronounced feature in many sections of solar dermatitis.

Chloroquin and quinacrine are satisfactory in treatment of mild cases of solar dermatitis. Hormone therapy is more effective in severe cases Males receive 500 I U of chorionic gonadotropic hormone daily or every other day for prolonged periods. Older males receive 50 mg testosterone weekly and V Fil creme Females receive 25-50 mg testosterone weekly with 0 25 Gm chloroquine twice a day

Polymorphous Light Eruption Some Unusual Reactions in Ultraviolet Light Test Sites are reported by Edwin J Levy Milton M Cahn and Bertram Shaffer (Univ of Pennsylvania) These reactions occurred in 4 of 27 patients with polymorphous light eruption tested with hot quartz ultraviolet light on the upper back. One patient showed persistence of erythema in test sites for 7 months after a single exposure. In another erythema persisted in test sites for 6 months faded, then spontaneously recurred. Chloroquine given concurrently suppressed polymorphous light eruption but had no effect on reaction at the test sites. The signifi

( ) J Invest Derm. 28 1 7 11, February 1957

cance of this persistent recurrent erythema is not known. It may represent a chronic dilatation of the minute blood vessels of the corium as a result of vascular damage from ultraviolet light

In 2 patients, typical polymorphous light eruption following sunlight exposure was accompanied by appearance of papules in previously tested sites which were not reexposed. Prior intense ultraviolet light exposures in the same test areas had resulted in no observable reaction in 1 patient, although a typical papular response was noted in the other These unusual papular reactions suggest that polymorphous light eruption is a true photoallergic disease. In 1 patient, a previously sensitized skin area reacted to an eliciting exposure at a distant site. In the other an incubation period presumably ensued before the sensitizing substance caused a reaction. The nature of the sensitizing substance is unknown. It has been hypothesized that proantigen, a precursor substance present in the skin of a photoallergic person, is transformed to antigen under the influence of irradiation.

► [The flaring up of areas previously exposed for testing with light after irradiation of a distant region with intense light is strongly reminiscent of a similar phenomenon seen in allergic eczematous contact dermatitis. In the latter condition, previously affected but healed sites sometimes flare after exposure of a distant site to the responsible allergen. We agree with Levy Cahn and Shaffer that if such a phenomenon exists, it speaks strongly in favor of an allergic mechanism having produced the reaction.—Eds.]

Diathetic Dermatoses and Parasympathetic Nervous System. The French school includes with the group of diathetic dermatoses Besnier's prurigo (atopic dermatitis) Darier's chronic diffuse prurigo simplex and the so-called diathetic eczema of the aged. In studying diathetic dermatoses, R. Aron Brunetière[2] (Paris) notes that several symptoms are often observed (1) chronic constipation (hyposthenic dyspepsia) which becomes worse during acute outbreaks of the dermatosis and is due to vagus hypofunction (2) faulty thermoregulation which causes patients to complain of shivering during hot weather and exacerbation during the winter also indicating defective vagal function (3) disturbances of sleep which are not caused solely by pruritus and which can usually be eliminated by parasympathicomimetics

Assuming that a permanent hypovagotonia with relative hypersympathicotonia exists in diathetic dermatoses the author gave a manganese-chlorine-acetylcholine preparation

(2) Ann. dermat. et syph. 83 485 500 Sept. Oct., 1956.

(MCA) to 16 patients with Besnier s prurigo 14 with Dar ier prurigo 7 with eczema of the aged and 2 with senile pruritus Occasionally neostigmine (an alkaloid of the physostigmine group) and geneserine (an alkaloid prepared from Calabar beans) were added to the MCA therapy Parenteral (subcutaneous) MCA was more effective than oral. For adults, the usual doses were 10 15 and 20 mg./day for 10 15 and 20 days, although 4 mg /day fo 6-8 weeks proved useful in 4 Children were given 4 mg mornings and evenings for 10 days.

N side ffects were observed. On the contrary the patients had feeling of well being and relaxation and appetite and sleep improved, the latter even before the pruritus subsided. Without any local treatment skin manifestations cleared or improved considerably in patients w th Besnier's prurigo (7 with ecurrences were cured when treatment was reinstituted) or Darier s prurigo (of 5 with recurrences 2 were cured by a second course of therapy) No recurrences were noted in the patients with diatheti eczema of the aged.

The results of acetylcholin therapy in diathetic dermatoses are remarkable because pathogenically the effects in dicat the existence of hypovagotonia and, nosologically that Besn er prurigo may be related to Darier s prurigo, which probably is a late form of the Besnier type, even in diathetic eczema of the aged. Etiologically the results seem to support the hypothesi of the all gic nature of diathetic dermatoses (Tzanck s vagotonia of allergics) Physiopathologically th results show that as a consequence of the vagosympathetic disequilibrium there appears to be a tendency to peripheral vasoconstriction. Results were good in patients with both Besnier and Darier type of prurigo and excellent in those with eczema of the aged and senile pruritus.

* [W are not certain that all the cases studied by the author actually belong in the group of eruptions which American dermatologists call atopic dermatitis

Among the many stigmas which characterize patients with atopic dermatitis are some hich point in the direction of autonomic nervous system imbalance In our case material, however we have not been impressed with particularly frequent occurrence of such manifestations as constipation, disturbance of sleep (not due to itching) and shivering during hot weather —Eds]

Studies on Vascular Skin Responses in Atopic Dermatitis Influence of Psychologic Factors are reported by F Kal E D Wittkower G W Vavruska, P Telner and S Fergu

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(2) Ann. dermat. et syph. 83 485 500 Sept.-Oct., 1956.

Method.—Eight subjects were selected who gave strong positive tests to one or more atopens. None had atopic dermatitis. However 5 had bronchial asthma, 1 had hay fever and 1 had a h story of acute urticaria. All were sensitive to hus antigens. Therefore a patch of contact dermatitis could be provoked by patch tests with pentadecyl catechol, one of the antigens of the poison ivy plant. Specific atopens were given by different routes and effect on the experimental contact dermatitis was observed.

It was found that intranasal, subcutaneous and surface application of specific protein allergens caused an existing area of contact dermatitis to flare in some of the subjects who re acted with wheals to scratch tests with atopens In some, healing was considerably delayed and lichenification resulted from scratching Thus, the original contact dermatitis ac quired the typical characteristics of a local zed neuroderma titis During admi stration of the atopens, the skin reacted with inflammation to quantities of contact antigen that previously were innocuous.

The authors suggest that protein antigens, such as found foods, pollens and molds, are not primarily capable of ex citing the eczematous or dermatitic reaction but rather are secondary agents that can produce exacerbation n previously damaged skin sites, whatever their origin.

Cause of atopic dermat tis is unknown It occurs o er whelmingly but ot exclusiv ly in atopic persons but the dermatitis   not primarily the result of an atop reaction. It follows from this that con entional management—a oid ance of allergens and hyposensitization—ordinarily has l t tle ffect on the course of the disease Howe er there is a mall group f patients with atopic dermatitis probably not mo e than 5% in whom flare ups may be r lated to exposure to t pic allergens It s only n th s minority that the mechanism presented here appears to be operati e The original cause of th haracteristic dermatitis, even in this group re main u disclosed, d exacerbations fter exposure to the pec fi allergens are l mited exclusively to previously n volved ites. Protraction of the dermat tis a d transforma tion into persistent neurodermatit through scratching may be attributable to repeated exposure to topens.

Hyposensitization may be ndicated in such cases of atopic dermatitis and n certain hand eczemas nd other dermatitic reactions, f   the specific cases it can be hown that exacer bations follow exposure to the protein antigen The mech-

son[3] (McGill Univ.). Of 32 patients tested with an intradermal injection of histamine, 14 had skin response within normal range although the flare was pale and small in most. Abnormal skin response consisting of formation of a normal wheal without a flare was noted in 15 patients. In some blanching occurred around the wheal instead of the normal reflex erythema. Three patients varied in response between presence and absence of flare. Patients with abnormal skin response differed from those with normal reactions in the severity of their cutaneous symptoms; they showed higher incidence of severe extensive skin lesions, more relapses and were more resistant to therapy.

Psychiatric observation indicated that patients with normal response to intradermal histamine tended to display their emotions freely, especially aggressive drives. Patients with absent histamine flare showed a tendency to restrain a display of their emotions and aggressive drives. Those with a normal histamine response showed a significant and repeatable alteration in size of the flare concomitant with changes in their emotional state. All with abnormal histamine response (absence of flare) showed a flare when retested after an interview directed to relieve and discharge previously inhibited aggression.

The positive correlation between abnormal response and severity of the skin symptoms on the one hand and the degree and type of the psychologic disturbance of the patient on the other offers some practical means for roughly assessing severity of the psychologic disturbance and status of the disease by a simple intradermal test. Further observations are necessary to determine the accuracy of any prognostic conclusions derived from type of flare response and significance of normalization of skin response after therapy.

► [These variations in response to intradermal injections of histamine must be due to local vascular action, perhaps mediated by a substance via the blood stream. In the discussion of this paper it was stressed by Rothman and Dobson that there is no change in the skin blanching reaction after lumbar sympathectomy and brachial plexus block. This appears to rule out the nervous system as playing a role in the altered local skin response.—Eds.]

Relationship of Atopic Allergy and Dermatitis was investigated by John S. Strauss and Albert M. Kligman (Univ. of Pennsylvania).

(3) J. Invest. Dermat. 29: 67-80, August, 1957.
(4) A.M.A. Arch. Dermat. 75: 806-811, June, 1957.

The hereditary factor in neurodermatitis is recognized, as is the psychodynamic significance that parents who have had skin disorders react differently from normal people to skin disorders in their children. In atopic disorders there may be a specific reaction stress which occurs in hereditarily predisposed persons. Psychologic evidence in adult patients of sadomasochism, narcissism and exhibitionism are correlated with the skin symptomatology, but the authors believe that they are not etiologically significant. These disorders of adaptation can be triggered off by emotional or physiologic stress or certain allergens.

► [The authors call attention to the important role that heredity plays in the occurrence of atopic dermatitis (present in 19 of the 22 cases studied). Their approach appears much more reasonable than that of many others who have discussed the role of emotional factors in atopic dermatitis as they are willing to admit the role of the many other factors contributing to outbreaks and flare-ups, which must be given consideration. One might ask in view of the broad nature of the psychologic disorders suffered by the mothers of the affected children whether there is anything specific in them for atopic dermatitis. Also, are there not paternal influences? Apparently the fathers were not interviewed. Are not the fathers influenced from time to time by similar personal and family problems as the mothers and children. Unfortunately this study, as so many others in this field, is uncontrolled. Therefore, nobody knows what would have been the findings regarding the relationship of psychogenic influences to the outbreaks of other dermatoses with genetic background and of dermatoses without such background.—Eds.]

Hypogammaglobulinemia in Infantile Eczema. Electrophoretic studies of serum lipids and proteins were carried out in 247 infants with eczema by Jaroslav Horacek[4] (Children's Hosp., Brno). Hypogammaglobulinemia was found in 12 patients. The clinical picture in these patients was characterized by an acute onset of eczema associated with diarrhea, hypochromic anemia, leukocytosis often as high as 16,000-20,000 and, in most severe instances, enlargement of spleen and liver.

Serum lipids were frequently within normal limits. Total proteins showed very little variation in the course of the disease; however, considerable variations were found in alpha and gamma fractions. Normal values of gamma globulins in 90 healthy infants were found to be 11.9-16.6% at age 3 months, 10.1-14.3% at 6 months, 11.1-15% at 9 months and 14.8-18.5% at 12 months. In 4 illustrative cases the lowest values for gamma globulins were 11.8% and 10.6% at the age of 5 and ... months, 6.5% at the age of 5 months, 8.6% at

(4) Ceskoslov. dermat. 32: 10, 1957

anism of the commonly observed exacerbation of dermatitis during an attempt at hyposensitization is suggested from results of the present experiments

► [The cause of atopic dermatitis is still not completely elucidated. However much has been learned since the days of Besnier about stigmas that characterize patients affected by this dermatosis. Among these is the atopic hereditary background that can be shown in 80% of cases and that justifies the modern term atopic dermatitis, originated by Coca and Sulzberger. This atopic background manifests, among other features, what appears to be clinically a sensitivity to certain foods, inhalants etc. Most dermatologists would agree that the existence of such hypersensitivity clinically, perhaps with the exception of wool and dust, can be reliably demonstrated only in a small minority of cases. Moreover in those patients in whom flare ups can be deliberately engendered with atopens, only improvement, but not cure, results from their avoidance. This makes it likely that even in these particular patients the allergic hypersensitivity is only part of the mechanism producing the disease.

The demonstration by Strauss and Kligman that interaction of atopen and atopic reagin produces flare-ups at the sites of contact dermatitis does not rule out the possibility that flare ups due to this interaction could occur also without pre-existing inflammation. The editors have observed in a few cases specific flare-ups in sites that, clinically at least, appeared normal before administration of the allergen. It should also be noted that F Herrmann was able to produce areas presenting the clinical changes of atopic dermatitis, when he injected the atopen in the normal-appearing skin of sensitive persons.

It is our conclusion that clinically hypersensitivity to atopens can become manifest via any one of these three pathways.—Eds.]

Mother-Child Relationship in Genesis of Neurodermatitis was explored and the stresses involved evaluated by Judd Marmor Milton Ashley Norman Tabachnick Margaret Storkan and Franklin McDonald[5] (Los Angeles County Gen'l Hosp.) The technic of "associative anamnesis" was used in interviews with mothers of patients with neurodermatitis to determine the circumstances and emotional climate under which the disorder first appeared. Three projective psychologic tests were also given to 10 of the 22 mothers (1) Draw A Person Test with Inquiry (Machover) (2) Forer Sentence Completion Test and (3) Thematic Apperception Test.

In all instances just before onset of the disorder the child was rejected or neglected by the mother (13) or fortuitously separated from her (9) by work or illness. All mothers given the psychologic tests were shown to be emotionally immature frustrated and overtly or covertly hostile to their husbands. Interplay of social and economic factors was often noteworthy particularly poverty and in 11 instances marital friction.

(5) A.M.A. Arch. Dermat. 74 599-603 December 1956.

3 DRUG ERUPTIONS

Ultraviolet Light Factor in Chlorpromazine Dermatitis. To determine what light factor may cause dermatitis in some patients receiving chlorpromazine, Milton M Cahn and Edwin J Levy[4] (Univ of Pennsylvania) studied 10 patients receiving chlorpromazine (5 with history of dermatitis following exposure to sunlight and 5 without) and 5 controls, e non-photosensitive persons not receiving chlorpromazine. All 15 subjects were exposed to ultraviolet light produced by a hot quartz mercury arc lamp There was no significant difference in the dose of ultraviolet light required t produce minimal erythema in any subject tested.

Reactions of photosensitivity to chlorpromazine developed only on exposure to intense summer sunlight containing ultraviolet wavelengths of between approximately 3,025 A and 2,968 A. As the patients did not react to hot quartz ultraviolet light which lacks this spectrum it seems that it this narrow band of light rays which induces skin reactions. Since these wavelengths are present only in summer sunlight and since the skin reaction is transitory photosensitivity resulting from chlorpromazine therapy need not be an indication for stopping the drug To avoid possible photosensitivity reactions, patients taking chlorpromazine should avoid undue exposure to summer sunlight.

► [It is interesting that such a small spectrum of ultraviolet light—3,025A to 2,968A—should be responsible for photosensitivity reactions of the skin due to chlorpromazine. The findings of John H. Epstein and co-workers (see following article) based on studies done with carbon arc lamp, support the conclusions of Cahn and Levy

Photosensitization dermatitis has often been seen after topical application of Phenergan which is chemically closely related to chlorpromazine At recent meeting, Stephen Epstein also reported having observed several cases of photosensitization dermatitis due to systemically administered Phenergan —Eds]

Study of Photosensitivity Occurring with Chlorpromazine Therapy s reported by John H Epstein, Louis A. Brunsting Marion C Petersen and Bert E. Schwartz[5] (Mayo Clin and Found.) Of 72 patients under chlorpromazine therapy 9 showed abnormal reactions in test sites to ultra

(4) A.M.A. Arch. Dermat 75:38-40, January, 1957
(5) J Invest. Dermat. 28:329-338, May 1957

1 year and 8.4% at 5 months. *These patients were susceptible* to pyogenic infections and were resistant to all forms of therapy. Follow up studies revealed that they achieved normal values for gamma globulins much later than normal infants. Sudden increase in gamma globulins from 8.4 to 21% was observed in the last *patient after recovery from otitis* media at age 1 year. This increase was accompanied by permanent improvement of eczema. The observations suggested that the cause of hypogammaglobulinemia in these infants was a constitutional delay rather than an inborn error of protein metabolism.

► [It appears likely that a 5% incidence of hypogammaglobulinemia in infantile eczema is more than coincidence. Perhaps the very distinct susceptibility of infants (and older human beings) with atopic dermatitis to cutaneous virus infections (herpes simplex, vaccinia) is in some instances due to hypogammaglobulinemia. There is at least one report of generalized vaccinia with fatal outcome which was attributed to agammaglobulinemia.—*Eds.*]

Ability of Skin of Infants and Young Children to Fix Skin-Sensitizing Antibodies. Passive Transfer by Method of Prausnitz-Küstner. The method presumably involves fixation of skin sensitizing antibodies to the endothelial cells of *the cutaneous vessels. Presence of a normal functioning* capillary network is necessary for appearance of the wheals that are characteristic of positive reaction. Ability of the skin of children to accept atopic allergens apparently has not been previously investigated, so Tage Samsøe-Jensen and Kristine Hauge Kristensen[7] (Sundby Hosp., Copenhagen) tested 105 premature and full term newborns and children under age 2.

A 10% solution of dried serum containing grass pollen antibodies was used. Individual reactions were pronounced and no subject failed to react. From a statistical computation increasing cutaneous reactivity, as shown by the size of the wheals, was demonstrated with increasing weight of the child. *It is suggested that this phenomenon may be due to* gradual anatomic and physiologic maturation of the skin, perhaps especially of the capillary network.

► [It is well known that infants have the capacity to produce Prausnitz-Küstner antibodies. This study shows that their skin also has the capacity to fix passively transferred antibodies. It was previously known that the skin of newborn *infants only a few hours old already has the capacity to* respond with whealing to stimulation with primary urticariogenic agents. —Eds.]

(7) Acta allergol. 11: 28-36, 1957.

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(8) A M A Arch Dermat 75 38-44, January, 1957
(9) J Invest. Dermat 28 129-138, May [illegible]

violet rays in the spectral zone below 3 100 A. These reactions appeared to be exaggerations of the normal sunburn response. A 1% solution of chlorpromazine hydrochloride examined spectrophotometrically showed complete absorption of the wavelengths between 2 000 and 3,700 A. Thus the absorption pattern of the drug included the ultraviolet rays shorter than 3 100 A.

Seven of the patients had maculopapular somewhat urticarial eruptions while taking the drug The eruptions appeared between the 7th and 14th day of therapy and lasted 5 31 days In 1 patient, the eruption cleared before the drug was discontinued and 2 showed pronounced accentuation of the lesions over the exposed parts

Examination of the urine of the 19 patients with abnormal reactions to ultraviolet rays revealed no abnormal porphyrins Weakly positive reactions for porphobilinogen were noted in specimens from 13 of the subjects but in 9 these reactions were found regardless of chlorpromazine intake None showed clinical evidence of hepatic dysfunction or porphyria

Since chlorpromazine is closely related to phenothiazine and Phenergan* which are well known photosensitizers, production of photosensitivity by this drug is not altogether unexpected. However the mechanism for the abnormal reactions to the sun induced by these substances has not been definitely determined. Ultraviolet rays with wavelengths shorter than 3 100 A are not likely to be involved in photodynamic reactions However since the absorption spectrum of chlorpromazine includes these short rays the drug could act as a light absorber for some photochemical reaction (probably not photodynamic in nature) This would require permeation of the drug into the epidermis

On the other hand chlorpromazine or its transformation products might act directly on the epidermal cells Such direct action also would necessitate that the drug or its metabolic products reach the epidermis Another possible mechanism of this exaggerated sunburn reaction may be related to the potent effect of chlorpromazine on blood vessels The drug appears to cause vasodilatation through central and peripheral actions. Since the erythema noted in the normal sunburn response is due to dilatation of the dermal blood vessels, a substance that would tend to enhance this vasodila

tation might conceivably cause an exaggerated response.

► [The possibility of photoallergic process also must be considered. Onset after 7 14 days may be due to cumulative effect. On the other hand, it also may be evidence that the incubation period of sensitization has passed. —Eds.]

Photoallergic Dermatitis Due to Nadisan. Sulfanilamide exanthems are often seen in skin areas exposed to light. The photoallergic nature of these eruptions may be confirmed by animal experiments and by exposing patch-tested areas to light (irradiated patch testing method) W. Burckhardt and K. and M. Schwarz Speck[1] (Univ of Zurich) report 2 cases of photoallergic dermatitis caused by nadisan which like many similar preparations is a sulfanilamide derivative and often used as peroral antidiabetic medication.

CASE 1 —Man, 80, treated for diabetes mellitus with nadisan, after exposure to sunlight (gardening) had an eruption limited to the exposed areas. On the face, neck, forearms and hands, edematous swelling, redness, blistering and oozing were soon followed by crusting and fissuring. After discontinuation of nadisan, mild antieczematous treatment and dark room therapy healing occurred within 3 weeks. Skin tests with 5% alcoholic solution of nadisan were negative, but the skin showed redness, swelling and papules after exposure to sunlight for 20 minutes. Of 2 patch tests with oxidation products of sulfanilamide, with 1% p-hydroxylaminobenzolsulfonicacidamide was strongly positive and the other with hydroxylated sulfanilamide in m-position was negative. Patch tests, irradiated and unirradiated, with another peroral antidiabetic medication artosin, (N-[4-methyl benzolsulfonyl]-N -butylcarbamide) were negative.

CASE 2 —Patient, 55, in 1944 had bullous dermatitis after applying an ointment containing Cibazol, which is also a sulfonamide. In 1950, he had paralytic face eczema. In 1956, after 10 days of peroral antidiabetic treatment with nadisan, he was hospitalized because of erythematous dermatitis of the face, neck and hands, edema of the eyelids and bullae on the dorsum of the hands and wrists. Nadisan was discontinued, dressings of boric acid solution and unguentolan were applied and he improved within 10 days.

Patch tests with 1% nadisan, 1% sulfanilamide, and 1% artosin gave negative results. Using a Kromayer lamp, filter permeable between 3,120 and 5,000 A at 2 cm. distance for 15 minutes, patch testing with 1% nadisan produced slight redness and infiltration whereas sulfanilamide produced marked redness, swelling and papules. p-hydroxylaminobenzolsulfonicacidamide caused an intense eczematous reaction with redness, swelling, numerous papules and blisters. The reaction to artosin and light was negative.

In these 2 patients the photoallergic character of the eruption following nadisan medication was established with the aid of irradiated patch tests. The antigen was probably

(1) Schweiz. med. Wchnschr. 87 954-956, July 1957

an oxidation product of the sulfanilamide derivative nadisan which formed in the skin after exposure to light No photoallergy resulted from the use of artosin another peroral antidiabetic sulfanilamide derivative in which the sulfanilamide character was eliminated by substituting the amino group in paraposition by a methyl group It is, therefore possible, to replace in peroral antidiabetic treatment the sulfonamides BZ 55 nadisan nidosan invenol fresan glucidoral orabetic carbutamide by methylated products D-860 artosin Rastinon Orinase* tolbutamide or glucophren

Acute Porphyria and Coproporphyrinuria Following Chloroquine Report of Two Cases is presented by Michael J Davis and Darl E. Vander Ploeg[2] (Brooke Army Hosp)

CASE 1—Man 35 was given chloroquine 0.5 Gm. daily for treatment of discoid lupus erythematosus. Nausea and anorexia developed on the 3d day and the patient began to pass red urine. No occult blood was noted in the urine. Urine urobilinogen was positive at 1.50 dilution. A 24-hour specimen contained coproporphyrin 2,951 mg and total uroporphyrins 20.2 mg Porphobilinogen was positive. Urinary porphyrins gradually decreased, and after 1 month the uroporphyrin excreted/24 hours was 0.4 mg Shortly after admission, the sulfobromophthalein test showed 47.5% dye retention serum bilirubin 3 4 mg thymol turbidity 5 5 units Three weeks later the liver function tests were normal except for 16.1% dye retention. Liver biopsy revealed Laennec's cirrhosis. Past history revealed heavy consumption of alcohol for 10 or 12 yrs.

CASE 2.—Man, 49 was given chloroquine 0.5 Gm. daily because of history of blisters on the dorsa of the hands after exposure to the sun and occasionally after trauma. A 12-hour urine specimen on admission contained 1 127 mg coproporphyrin and no porphobilinogen or uroporphyrin. The next day nausea and vomiting developed and the urine was dark red. On the day before admission the patient had generalized abdominal cramping and vomited some coffee-ground material He had consumed alcohol regularly for 20 years and rarely drank less than 6 cans of beer a day The patient became asymptomatic 24 hours after chloroquine was discontinued and left the hospital against advice before further studies could be performed. Six weeks later the urine contained only traces of coproporphyrin Liver function studies [illegible] in 48 hours thymol tur[illegible] [illegible] den Bergh direct 0.2 mg [illegible] 60%

The first patient had both cutaneous manifestations and abdominal signs and probably represents an example of the mixed type of hepatic porphyria He had liver disease of long standing and chloroquine probably precipitated an episode of hepatic insufficiency

(2) A.M.A. Arch. Dermat. 75 794-800, June, 1957

The second patient appeared to have porphyria cutanea tarda clinically but uroporphyrins were not shown. It has been reported that in some instances uroporphyrin may be absent from the urine and feces of patients with porphyria cutanea tarda. Had it been poss ble to follow this patient longer ntermittent excretion of uroporphyrin might have been shown

The authors suggest that before chloroquine is given, t d es for urinary porphyrins should be performed on pa tients with cutaneous manifestations of sun sensitivity or with hepatic disease.

► [This study suggests that asking patients concerning their drinking habits, past and present, could be simple, inexpensive approach to minimizing the chances of precipitating acute porphyria and coproporphyrinuria by administration of chloroquine —Eds.]

Cutaneous Test with Friction in Fixed Erythema due to a pecific drug was evaluated in 12 patients by Antar Padilha Gonçalves[3] (Uni of Rio de Janeiro) The offending substance previously dentified by oral administration n 10 patients was a barbiturate (Veronal 6, Dial 2 and Luminal® 2) th others were sen it ve to phenolphthalein and amidopyrine respectively Propylene glycol proved to be superior t l qu d petrolatum and normal saline solution as a sol ent for the drugs. Concentrations used were 3% for the barb turates 5% for phenolphthalein and 10% for am dopy n 7% aspirin was used in 1 case as a control Friction was produced by rubbing a piec of cotton saturated with the test solution on skin a eas which had previously e hibited the eruption for 1 minute ı tact areas were also tested s controls. Results were confirmed by repeated tests in most n tances.

All friction tests were negative in 8 cases. Two positive reactions were obtained with Veronal and 2 with Dial® but only n areas prev ously in ol ed in the fixed eruption. The eaction began 3-4 hou after friction, attained a maximum 9-11 hours later and disappeared in 24-48 hours. They appeared a erythema, with or w thout edema, sometimes accompanied by moderate stinging or itching There was no s temic reaction nor distant flare-up indicating that the mount of drug absorbed was small and that the procedu e w therefore les dangerous than oral or parenteral testing An attempt to potentiate the reaction by preceding the spe-

(3) Am. J. Dermat. ... 111-114 September 1954.

an oxidation product of the sulfanilamide derivative nadisan which formed in the skin after exposure to light. No photoallergy resulted from the use of artosin another peroral antidiabetic sulfanilamide derivative in which the sulfanilamide character was eliminated by substituting the amino group in paraposition by a methyl group It is, therefore, possible to replace in peroral antidiabetic treatment the sulfonamides BZ 55 nadisan nidosan invenol fresan glucidoral orabetic carbutamide by methylated products D-860 artosin, Restinon Orinase® tolbutamide or glucophren

Acute Porphyria and Coproporphyrinuria Following Chloroquine Report of Two Cases is presented by Michael J Davis and Darl E Vander Ploeg[1] (Brooke Army Hosp)

CASE 1—Man, 35 was given chloroquine 0.5 Gm. daily for treatment of discoid lupus erythematosus. Nausea and anorexia developed on the 3d day and the patient began to pass red urine. No occult blood was noted in the urine. Urine urobilinogen was positive at 1 50 dilution. A 24-hour specimen contained coproporphyrin 2,951 mg and total uroporphyrins 20.2 mg Porphobilinogen was positive. Urinary porphyrins gradually decreased, and after 1 month the uroporphyrin excreted/24 hours was 0.4 mg Shortly after admission, the sulfobromophthalein test showed 47 5% dye retention serum bilirubin 3 4 mg thymol turbidity 5.5 units. Three weeks later the liver function tests were normal except for 16.1% dye retention. Liver biopsy revealed Laennec s cirrhosis. Past history revealed heavy consumption of alcohol for 10 or 12 yrs.

CASE 2—Man, 49 was given chloroquine 0.5 Gm. daily because of history of blisters on the dorsa of the hands after exposure to the sun and occasionally after trauma. A 12 hour urine specimen on admission contained 1 127 mg coproporphyrin and no porphobilinogen or uroporphyrin. The next day nausea and vomiting developed and the urine was dark red. On the day before admission the patient had generalized abdominal cramping and vomited some coffee-ground material. He had consumed alcohol regularly for 20 years and rarely drank less than 6 cans of beer a day The patient became asymptomatic 24 hours after chloroquine was discontinued and left the hospital against advice, before further studies could be performed. Six weeks later the urine contained only traces of coproporphyrin. Liver function studies showed cephalin cholesterol flocculat on 3+ in 48 hour thymol turbidity 7.6 units serum bilirubin 0.3 mg van den Bergh direct 0.2 mg indirect 0 1 mg total cholesterol 143 esters 60%

The first patient had both cutaneous manifestations and abdominal signs and probably represents an example of the mixed type of hepatic porphyria He had liver disease of long standing and chloroquine probably precipitated an episode of hepatic insufficiency

(1) A.M.A. Arch. Dermat. 75 796 800, June 1957

with penicillin sensitivity tuberculin type reactions were observed after intradermal injection of this drug In 2 with dermatitis, testing gave no information. However in these 2, and in 1 other platelet count dropped significantly after penicillin was given, indicating that this material was responsible for the symptoms.

In 3 urticaria patients fairly severe systemic reactions were provoked by testing Delayed responses to penicillin testing were observed occasionally in normal subjects when 10,000 units was injected. However no reaction, immediate or delayed, was observed when only 100 units was used in testing Nilzén s opinion is that response to 100 units is significant, b t response to 1,000 units may be nonspecific.

Desensitization to penicillin was successful in some patients with dermatitis due to this drug, but was less often successful in patients with urticaria.

► [Obviously no one test can be relied on to indicate whether person is allergic to penicillin in one form or another Therefore, it seems sensible to subject patients ith suspected allergy to penicillin to battery of tests, including the patch test, intracutaneous test for the immediate and delayed reaction, platelet count, nephelometric tests and others It should be noted that Nilzén was successful in hyposensitizing patients with penicillin dermatitis but less so with penicillin urticaria —Eds.]

Erythema Multiforme Following Poliomyelitis Vaccination Report of Case is presented by Paul Chervinsky[5] (St. Luke s Hosp New Bedford Mass)

Girl, 9 had a pruritic erythematous eruption with indefinite margins on the thighs, abdomen, chest and hands. The eruption appeared 2 weeks after first dose of Salk vaccine. A few days later it became scaly and had disappeared completely when the patient was examined 2 weeks after onset.

Fiv weeks after the first dose of Salk vaccine was given, a second injection (0 1 cc ntradermally) was given. There was no local reaction, but 3 days later joint pains and severe generalized pruritus were noted Within 24 hours the body was covered with an erythematous, raised eruption especially marked on the thighs, abdomen, face and arms The eyelids were edematous.

Orange juice had, on several occasions, produced a pruritic, maculopapular dermatitis on the thighs. This had been carefully a oided. There was no history of injection of foreign serum proteins. The patient had had penicillin injections in the past with no untoward symptoms

It mpossible to be certain that this reaction was due to a component of the poliomyelitis vaccine, but the time relation makes t probable. Skin tests are not absolute indications of penicillin sensitivity and th lack of any local eaction to

(5) Ann Allergy 15 30-31, Jan Feb, 1957

cific test with an application by similar friction of a solution of cortisone in propylene glycol yielded inconclusive results.

These 4 reactions were interpreted as specific, since they were identical with those previously obtained in oral tests. The results indicate that the shock tissue is deeper than the epidermis since in some patients tests were positive in thin skinned areas such as the lower lip and palmar surface of the wrist, and negative on the palm

Obviously this friction test cannot replace oral and parenteral testing since a false negative response was obtained in two thirds of the patients. Nevertheless in severe cases, the test might be used first with the hope of avoiding the more serious reactions that occur with other methods.

► It is unusual that a specific reaction can be elicited with inunction or injection of the causal drug in fixed drug eruptions.

Although it is true that the shock tissue in fixed drug eruptions is most likely in the cutis, the fact that the "rubbing" test was positive in "thin-skinned" areas in contrast to negative responses on the "thick-skinned" palms does not necessarily denote that the shock tissue is located deeper than in the epidermis. The reason why the palms may not respond is more likely to be that the allergen fails to penetrate the palmar epidermis, not only because of its thickness but also because of the absence of the pilosebaceous unit which affords additional avenues for penetration.—Eds.]

Penicillin Allergy Åke Nilzén[4] (Stockholm) tested 27 patients with sensitivity to penicillin and/or procaine using patch tests scratch tests and intradermal tests In several patients platelet counts were made after administration of the allergen Of 15 patients with urticaria 10 were sensitive to penicillin and 5 to procaine Only 4 of these patients had immediate urticarial reactions to the scratch test Delayed response after intracutaneous injection of penicillin was observed in 7 of the 10 patients sensitive to this drug This test was not used in those sensitive to procaine only Two of the 10 patients sensitive to penicillin and all 5 with urticaria due to procaine showed eczema type reactions to patch tests A drop in platelet count after administration of the causative allergen was observed in 5 of 6 patients with urticaria so tested

Contact type dermatitis was present in 14 patients In 9 symptoms were due to penicillin and in 5 procaine was the offender The patch test in these patients as was expected was superior to other testing procedures it was positive in 6 penicillin cases and in all 5 procaine cases. In 4 patients

(4) Acta dermat.-venereol. 36:389-393 1956.

sorbed drug averages 150-300 mg which corresponds to a daily intake of 65-140 mg bromine.

Among 84 patients treated longer than 4 years and 13 others treated less than 1 year typical acne developed in 1 patient only after 18 months of therapy Papular and papulopustular eruptions developed on lateral parts of the forehead, cheeks and chin and the skin at the sites of injection was slightly eddened Two weeks after appearance of the eruptions, the patient developed profuse rhinitis. Two other patients developed brownish papular and macular eruptions which were not typical enough to be attributed to bromine. B omine intoxication occurs rarely after administration of organic salts, but impaired renal function n patients with hypertension and limitation of sodium intake might lead to increase in bromine retention. The filtration rate in the patient with bromine acne was only 33 4 ml

► [The fact that only 1 patient in this series had an acneform eruption after ingestion of drug containing bromide should not be reason to cease questioning patients concerning the possible role of halogens (iodides and bromides) in acneform and other dermatoses.

There are at least tw sources of halogens which are often overlooked in searching for exposures to iodides or bromides in patients with acneform eruptions, dermatitis herpetiformis and other eruptions which are suspected of being due to these halogens or of being aggravated by them. One of these sources is itamin and mineral dietary supplements which almost regularly contain iodides The other is drugs hich are not considered bromides in the usual sense, but which are bromide salts of such compounds as Banthine scopolamine, etc. W have seen number of patients in whom the history and clinical signs strongly implicated such forms of iodides or bromides ingested as the cause of their eruption or as aggravating factors.—Eds]

Toxic Epidermal Necrolysis Eruption Resembling Scalding of Skin reported by Alan Lyell (Royal Infirm Aberdeen) in 4 patients Each patient experienced short lived prodromal ymptoms pparently due to toxemia. These were followed by erythema and kin tenderness, and in turn, by peeling of large a eas, exposi g a dark red, excessively tender urface which healed rapidly without scar In 3 patients, fluid collected beneath the loose skin forming flaccid blisters. The linical resemblan e to scalding was close both in appearance of the lesions and sensations of the patients How there w no hock or exudation such as occurs after scalding

Th pathogenesis of the syndrome is epidermal necros s, m. d.rt. action to reactions, s ch as erythema mult forme

[1] Brit J Dermat. 68 355-361, November 1956.

the intradermal injection of the vaccine showed it to be of little immediate value in predicting a systemic reaction

[In several cases seen by the editors it has also been difficult to decide whether the presenting eruption was due to poliomyelitis or influenza vaccine or some other cause. The time relation between injection of one of these vaccines and onset of the eruption, as well as other features of these cases, strongly suggested that the eruption was due to the vaccine The lesions clinically resembled erythema multiforme and pityriasis rosea

Adoni and Tschan (J.A.M.A 164 205 May 11 1957) report a case in which attacks of herpes simplex ceased after 2 standard dose injections of poliomyelitis vaccine. It will be worthwhile watching to see whether there are any more beneficial reactions resulting from poliomyel tis or influenza vaccine especially in recurrent herpes simplex, aphthous stomatitis and other conditions associated with virus infections.—Eds.]

Rheumatoid and Lupus Erythematosus like Syndromes Complications of Hydralazine (Apresoline®) Therapy for Hypertension are reported by J Gordon Erickson Edgar A. *Hines Jr Gertrude L Pease and Louis A Brunsting*[6] (Mayo Clinic and Found) Of 8 patients from a group of more than 200 who received 200-800 mg hydralazine daily for hypertension 5 had severe and 2 moderately severe rheumatoid symptoms and 1 had severe leukopenia Of the 5 with severe rheumatoid symptoms 4 had a positive reaction to a 2-hour clot test using peripheral blood The other patients had negative or doubtful L.E. tests Symptom were present 1-6 months before hydralazine was discontinued After the drug was stopped the L E te t and the sedimentation rate were the last signs to return to normal Di continuing the drug was enough to hasten recovery without use of corti one or ACTH Two patients had excellent re ults from long term treatment with hydralazine with no untoward ymptom

Arthralgia myalgia fever skin eruption and other symptoms may indicate toxicity to hydralazine To decrease the toxic reactions of hydralazine smaller doses should be used plus other antihyperten ive drugs As soon a good control is established with hydralazine alone the dosage hould be reduced to under 400 mg /day It may be useful to withdraw hydralazine periodically for 3-4 day after the blood pressure is stabilized near the normoten ive range

Bromine Acne after Prolonged Administration of Pentamethonium. Occurrence of this type of acne was tudied by Otto Ripka and Richard Schwank[7] (Univ of Prague) Excretion studies after parenteral oral or rectal admini tration of pentamethonium demonstrated that the amount of ab

(6) A.M.A Arch Dermat 74 640 647 December 1 56.
(7) Ceskoslov dermat 32 152 155 June 1957

► [The rather sudden onset, rapid development and relatively quick clearing of the skin lesions, the association with systemic symptoms and with urticarial lesions in 1 case strongly suggest causation by drug

Dover' powders with aspirin had been taken by 1 and Butarolidin® by another patient before onset no history of drug ingestion was discovered in 2 other cases. The clinical lesions in these patients are strongly reminiscent of case of severe bullous drug eruption due to mercury which the editors saw some years ago. Their case was due to hypersensitivity to mercury and cleared rapidly after systemic administration of BAL.—Eds.]

Toxic Epidermal Necrolysis Report of Four Cases. One is described by R. Lang and Jean Walker[9] (Univ of Cape Town)

Negro man, 48, was unable to sleep because of shivering attacks and a generalized painful sensation in the skin after taking some laxative tablets containing phenolphthalein and aloin. The next morning he noticed dusky red patches scattered over the body and several large "blisters containing clear fluid. He was hospitalized 4 days later with a generalized eruption consisting of flat, well-defined, dusky purple areas, 5-10 mm in diameter In the axillae and groins and over the anterior aspects of the trunk and thighs, the epidermis was detached from the dermis and in some areas flaccid bullae had formed. Slight pressure on the bullae caused the fluid to raise further peripheral epidermis. Large areas were completely denuded, revealing pink surfaces which were exquisitely tender and exuded large amounts of serum.

An ointment containing Terramycin and balsam of Peru in sterile petrolatum was pplied to the involved areas and thick, firm bandages were used in the hope of checking the outpouring of serum. These were left in place for 5 days, only the outer coverings being changed when they became sodden. Cortisone and potassium chloride were administered orally Dextran was given intravenously 7 pints in the first 36 hours. A high-protein diet was prescribed, and Terramycin® was given in doses of 500 mg every 6 hours. The patient was discharged on the 12th day, skin surface was intact and the extensiv raw areas were covered with healthy though depigmented epithelium.

Toxic epidermal necrolysis appears to be a variant of erythema multiforme in which the epidermis is the target of a se ere toxemia. The striking difference between toxic epidermal ecrolysis and all other forms of erythema multiforme is th remarkable, sudden, painful epidermodermal cleavage which results in a clinical picture resembling scalding In 3 of th present cases the onset followed administration of a drug known to be toxic to certain persons.

► [The authors refer to the eruptions in their 4 cases as being an acute toxic syndrome of sudden dermoepidermal cleavage resembling scalding," this they call "toxic epidermal necrolysis. It is our impression that they may represent acute drug eruptions resulting from an allergic hypersensitivity If this is correct, the use of the words "toxic" and "toxemia in connection ith these eruptions appears ill advised —Eds.]

(9) South African M. J 31 713-716, July 20 1957

dermatitis herpetiformis and pemphigoid which depend on dermal inflammatory changes. Blisters are almost incidental to the syndrome Fluid fills the cleft formed by epidermolysis and since the amount of fluid is small in relation to the potential space, the blisters are flaccid can be spread readily by external pressure and often display fluid levels

Histologically the major damage is confined to the epidermis and consists of necrosis of the epidermal cells. In 1 patient the blister formed between the dermis and epidermis,

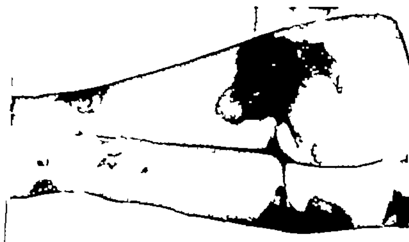


Fig. 6.—Skin eruption exposing dark red, raw tender surface resembling scalding (Courtesy of Lyell, A. Brit. J Dermat. 68:355-361 November 1956)

whereas in another the necrosis was intraepidermal This difference may be one of degree only

Woman, 34 had had 5 attacks of a blistering eruption always preceded by pain in the right loin. When first examined she had pain, but no skin eruption. Shortly thereafter a blotchy erythema appeared, mostly on the thighs and buttock The skin was tender and she felt ill and had a fever

The next day the red skin began to loosen and could be separated from the underlying dermis. Formation of blisters resulted from collection of fluid in the potential space beneath the loosened layer The epidermis in apparently unaffected neighboring areas could be loosened by the finger Soon the loose skin peeled off exposing a dark red raw tender surface (Fig 6) The t emia subsided rapidly and the patient soon felt well, although it took several weeks for the skin to heal.

Later the patient had another attack and still later she had hematemesis and angioneurotic edema after administration of Do er powder with aspirin for a backache. Although no cause was found for the cutaneous reactions, it is possible that the toxin in her case was a drug

acid preparations used in various dermatologic conditions was studied in 22 hospitalized patients. Boric acid was applied as a 5% ointment in white petrolatum, as a saturated solution and as pure boric acid crystals in such conditions as exfoliative dermatitis, dermatitis venenata, leg ulcers, mycosis fungoides and extensive ecthyma. Areas treated varied from 1 to 99% of the skin surface. A significant rise in blood boric acid levels was not noted in any patient after periods of 1-8 weeks. In most patients, rapid healing of the skin occurred during treatment with boric acid. Such healing would tend to prevent further absorption of the drug. In the fatal case reported, the skin condition grew worse during treatment, which would enhance absorption of boric acid. Possibly in some elimination of the drug is slower than normal.

The authors believe that boric acid preparations may be used safely in treatment of cutaneous diseases if they are not used indiscriminately. Pure boric acid powder or crystals should not be used. Extensive areas should not be treated for more than 1 week, particularly if the skin condition shows no sign of resolution. Physicians using the drug should be familiar with the symptoms of boric acid poisoning. Diagnosis of poisoning should not be made merely from the presence of boric acid in the urine. It is necessary to demonstrate toxic blood or tissue levels.

► [Certainly the weight of evidence, based on the frequency of external use of products containing boric acid for many years in probably hundreds of thousands of patients attests to the relative harmlessness of this chemical. On the other hand, there is the question as to the usefulness and effectiveness of this substance. Is boric acid ointment more effective than the ointment base alone and, if so, in which skin conditions. In our own practices, we hardly ever use boric acid ointment or wet compresses and actually could not miss it if it were no longer available.

In the discussion, Rothman remarked that even though he has "prescribed many kilograms and maybe tons of boric acid," he actually wondered if "boric acid wet packs are any better than saline solutions" and if "the addition of 1% or 5% boric acid to ointments or pastes makes any difference." We agree with Jordan and Crissey that use of boric acid is "a habit acquired from our predecessors."—Eds.]

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4. MISCELLANEOUS DERMATOSES

Incidence of Disseminated Lupus Erythematosus: Follow-up Studies Indicating Increased Frequency. Alma Svanborg and Lennart Solvell[1] estimated the incidence in Gote-

[1] J.A.M.A. 165: 126-128, Nov. 2, 1957.

Transient Depilatory Reaction and Other Untoward Effects of Desacetylmethylcolchicine (Colcemid[1]) are reported in 1 of 6 patients with gout by T E. Weiss and Albert Segaloff[1]

Man 50 with recurrent acute gouty arthritis for almost 10 years, *showed tophi on ears, hands and feet.* Treatment with colchicine had relieved gout but had produced toxic gastrointestinal manifestations. He was instructed to take 5 mg Colcemid every 8 hour for 3 doses. On his own initiative, he took an additional 5 mg 3 times a day for 7 days after which he noted drowsiness and numbness and tingling of the left hand and forearm He discontinued taking Colcemid After 5 days he lost large amounts of hair from the scalp The loss persisted for about 20 days until about 90% of the hair was gone the natural brown hairs being affected more than the gray Pubic and axillary hair was not affected, but there was no beard growth for about 10 days. Blood examination about 3 weeks after stopping Colcemid showed an abnormal differential picture with 1% myelocytes, 3% metamyelocytes, 12% bands, 42% segmenteds 1% basophils, 1% eosinophils, 30% lymphocytes and 10% monocytes

Alopecia reached a fixed state 3 weeks after onset. Shaving was performed every 2 or 3 days. Scalp hair began to reappear 8 weeks after discontinuing Colcemid* and was normal 5 months after onset of alopecia. When he was seen 15 months later the hair on the scalp and face was growing normally Gout was being controlled with 1/100 gr colchicine daily The left arm symptoms had disappeared.

The complications noted in this patient necessitate further evaluation of Colcemid* if it is to be used in treating gout.

Boric Acid Poisoning Report of Fatal Adult Case from Cutaneous Use Critical Evaluation of Use of This Drug in Dermatologic Practice is presented by James W Jordon and John T Crissey[2] (Univ of Buffalo)

Woman, 35 had a generalized eruption after treatment of a rash on the leg with an ointment containing ethyl aminobenzoate. Continuous wet dressings of saturated solution of boric acid were used for about 14 days when she became lethargic

She was hospitalized 24 hours later in deep coma. A generalized *erythema, with scaling was noted on the entire skin surface* The face and extremities were cyanotic the pupils did not react to light and blood pressure was unobtainable Pulse was 120 respiration 40, chest was clear and extremities were spastic She died 14 hours later

Autopsy revealed hyperemia of liver and lungs The glomerular loops of the kidneys were dilated and filled with blood. The tubules showed degeneration and necrosis. The bone marrow was hyperplastic, with predominance of the eosinophilic series. *Analysis for boric* acid showed liver 79 mg brain 69 mg urine 525 mg spinal fluid 95 mg and blood 350 mg./100 Gm.

Possibility of boron poisoning from absorption of boric

(1) Ochsner Clin. Rep. 3 21 23, January 1957
(2) A.M.A Arch. Dermat 75 720 728, May 1957

who received short courses of hormone therapy the disease flared up when the medications were discontinued before the natural remission occurred. In 5 patients steroid therapy was gradually discontinued, and its resumption was not necessary. Two patients did not require cortisone or ACTH for 2 years, when relapse occurred and hormone treatment was resumed.

One patient had severe leukopenia (800 leukocytes/cu mm.) 10 days after a second course of nitrogen mustard was given. Associated with the drop in leukocytes and other manifestations of impending agranulocytosis was a reversal of the L.E. test to negative. The test had remained negative for 6 years, and remission was complete except for persistently high sedimentation rate. After this success, 35 other patients were treated with nitrogen mustard. One died of agranulocytosis. The dosage was reduced in the other 34 without the side effects or the dramatic therapeutic effect noted in the first patient.

From a review of the case histories of the 12 seriously ill patients, several conclusions are drawn. Steroid therapy is indicated for as long as necessary to control the disease and until a natural remission occurs. Steroid therapy is not indicated in mild forms of the disease. With steroid therapy the instability of the disease can be controlled, permitting pregnancy and emergency major surgical procedures. Pregnancy, while not recommended because of additional technical burdens, should be permitted to go to term. Antimalarial drugs have a place in treatment of systemic and discoid lupus erythematosus. These drugs may permit moderate sun exposure in some patients. Laboratory procedures such as L.E. tests, serum electrophoretic patterns and urinalyses may show return to normal, but these improvements do not necessarily indicate permanent remission. Stable remissions may occur but true cures are doubtful.

► [It is becoming increasingly evident that another one of the heretofore fatal diseases has been tamed and no longer necessarily has fatal effects. Not only is the life of the patient saved, but such patients can now become pregnant without fear of having to have the pregnancy interrupted. However, one must not lose sight of the fact that all of this has been achieved with palliative therapy and that the problem of the basic etiology of lupus erythematosus remains unsolved.—Eds.]

Gastrointestinal Manifestations of Systemic Lupus Erythematosus were studied by Charles H. Brown, Earl K.

borg during three 2 year periods (1938-39 1948-49 and 1954-55) The case records of all patients with neuritis fever of unknown origin sepsis uncertain diagnosis and diseases of the heart blood vessels, joints and skin were reviewed. It was possible to trace all patients and diagnosis was verified by data from re-examination records of later hospitalizations or autopsy

There were 3 patients in 1938-39 and 3 in 1948-49 in whom disseminated lupus erythematosus might be suspected. Diagnosis in the material from these years was made even in doubtful cases on the basis of a study of the continued course of the disease. Diagnosis was established in only 1 of these patients at the time of hospitalization.

In 1954-55 there were 18 cases with a definite diagnosis. Diagnosis was established on the basis of a typical clinical picture and not on the basis of recently developed clinical aids such as the L.E. cell phenomenon It is highly probable that a review of these patients after 10 years would show an even higher incidence as the initial symptoms can be relatively insignificant As the increase in the number of cases cannot be accounted for by changes in the population of the community or the number of patients hospitalized it would seem that there has been a real increase in incidence

It is impossible to express a definite opinion as to the cause of the increase as long as the etiology of disseminated lupus erythematosus is uncertain If a toxic allergic or immunologic pathogenesis is accepted the fact that persons are increasingly in contact with such materials as sulfonamides, antibiotics preservatives and dyes might explain the increased incidence

► [As is well known, for many years, and long before the general medical public started to take an interest in its existence dermatologists have been familiar with the chronic discoid and acute systemic form of this disease. Perhaps the increasing awareness of physicians, in particular internists and general practitioners, of the signs and symptoms of disseminated lupus erythematosus, *together with improved methods of diagnosis*, accounts for the increased frequency with which the diagnosis is being made today in Sweden and elsewhere —Eds.]

Six Years Survival in Severe Systemic Lupus Erythematosus Analysis of 12 Cases is presented by John R Haserick[4] (Cleveland Clinic) *Only patients with disease so severe that they were not expected to live were included All but 1 received treatment with cortisone or ACTH In many patients*

(4) A.M.A. Arch. Dermat. 75 706 714 May 1957

litis n some patients must be considered. An L.E. test is ndicated in patients with atypical ulcerative colitis and in patients with systemic complications of ulcerative colitis

Autopsy done in 11 of the 87 patients revealed normal gastrointestinal findings in 9 interstitial edema and submucosal hemorrhage of the small intestine in 1 and collagen deposition in the submucosa of the stomach in 1 The autopsy findings provide no definite indications of the cause of ileus n the 5 patients.

Specificity of L.E. Cell Phenomenon was studied by Th. Inderbitzin and M Hunziker[8] (Univ of Zurich) Because phagocytic phenomena esembling L.E. cells (pseudo-L.E. cells) ha e been observed in various diseases, some authors ha e been doubtful whether L.E. cells are specific of acute disseminated lupus erythematosus. Pseudo-L.E. cells may be formed by phagocytosis of cellular or nuclear fragments of other cell but most of these fragments still show cellular or nuclear structu es, whereas in true L.E. cells, the origin f lusions from nuclear material can be demonstrated only b Feulgen stain g Pseudo-L.E. cells can also be caused by phagocytosi of amyloid, serum globulins precip tated in the serum (cryoglobulins) or by phagocytosis of erythrocytes by neutrophils The true L.E. c ll can be differentiated from pseudo-L.E. cell not only by morphologic o tinctorial peculiarities of inclusion bodies and by the causat ve serum factor but lso by the presence of transition forms, i.e., cells that still exhibit intracellular disintegration of nuclei

T find further support f r the belief that the L.E. cell phenomenon specific for acute d eminated lupus erythem to-u the authors tested 559 pat ent with high erythrocyte sedimentation rat and mor or less marked hyperglobu inemia because levated eryth ocyte sedimentation rate and hypergl bulinemia ar essential findings in acute dissemi nated lupu erythematosus and beca se the Haserick factor combines with the gamma globulin fraction. Positi e L.E. cell phenomenon was found in 10 patients of whom only 1 w hospitalized because of diagnosed acute disseminated lupu erythematosus, which was the primary diagnos s in al 5 of the other nonhospitalized patients. Clinical symptom included fever often of septic type rapidly increas g a thenia with weight loss arthriti and arthralgia chronic

[8] Dermatologica 113 373 389 December 1956.

Shirey and John R. Haserick[5] (Cleveland Clinic) Of 87 patients 55 had no abdominal complaints 25 had minor gastrointestinal symptoms requiring only symptomatic treatment and 7 had severe gastrointestinal symptoms that were among the predominant complaints and constituted major problems in diagnosis and treatment.

Of these 7 5 had poor peristaltic activity and lack of tone in the upper gastrointestinal tract, with symptoms and signs suggestive of obstruction although no obstructive lesions were present They were considered to have adynamic ileus for which no obvious cause could be found Presence of the ileus was confirmed by x ray (3 patients had dilated second and third parts of the duodenum 1 a dilated, atonic stomach and 1 segmental dilatation of the jejunum)

Ileus was temporary with symptoms subsiding and x-ray findings returning to normal The patient with jejunum involvement improved with surgical evacuation of the jejunum only Since ileus usually is temporary the authors believe that surgery should not be performed in these patients. The conditions of the 3 patients with duodenal and gastric ileus responded favorably to ulcer therapy One patient who did not receive ulcer therapy had a perforated ulcer without the usual signs and symptoms while on steroid therapy

The incidence of upper gastrointestinal ileus in this group of patients (5 of 87) is much greater than would be expected by chance and suggests that lupus erythematosus may be an etiologic factor in the ileus Collagen deposition in the submucosa vascular changes associated with the primary disease or a localized neurogenic phenomenon seems to be the most likely explanation for the ileus.

Two of the 7 patients also had chronic ulcerative colitis. This association is uncommon In 20 other patients with ulcerative colitis L.E. tests were negative Ulcerative colitis has much in common with systemic lupus erythemato us. Absence of the homogeneous ground glass sub tance vasculitis in some patients and systemic complications of chronic ulcerative colitis (rheumatoid arthritis erythema nodosum iritis and others) all suggest that this disea e may be a systemic or collagen disease similar to lupus erythematosus. Steroid therapy is helpful in both conditions The po ibility that systemic lupu erythematosus may cau e ulcerative co-

(5) Gastroenterology 31 649-666, December 1956.

each type was incubated in highly positive L.E. serums at temperatures between 18 and 38 C. and the nuclei then re moved by centrifugation, the serums lost completely their ability to induce L.E. cell formation. Electrophoretic and immunologic determination of total serum gamma globu lin before and after absorption with nuclei showed little change

Adherence of the serum factor to the nuclei is suggested by the fact that nuclei which had been removed from L.E. serum, washed with cold saline until the solution was free from protein and then incubated with fresh human white blood cells were readily phagocytized to form L.E. cells. Nuclei exposed to normal serum and treated in an identical manner were not similarly phagocytized.

In an effort to determine the reactive component of the nuclei similar experiments were done with isolated nuclear nucleoprotein After absorption with the nucleoprotein, L.E. serum was unable to induce L.E. cell formation. When the nucleoprotein, after incubation with L.E. serum, was washed and incubated with fresh white blood cells strands of nucleoprotein were phagocytized by the white blood cells to form inclusion bodies very similar to those of the L.E. cells.

After treatment with desoxyribonuclease sufficient to remove about 50% of the desoxyribonucleic acid (DNA) the nuclei would absorb some of the L.E. factor and would readily r lease all of that absorbed on subsequent incubation at 56 C. If all the DNA was removed none of the factor could be absorbed.

Exposu e of nuclei to normal serum, to cirrhotic serum with very high gamma globulin and to serum with large amounts of euglobulin did not make the nuclei susceptible to phagocytosis nor did it interfere with their ability to absorb L E. factor However absorption of factor was prevented by prior treatment of nuclei with protamine, which thought to bind the phosphate groups of DNA and with Atabrine

Slides containi g L E cells were reacted with fluorescent rabbit antiserum to normal human gamma globulin. Nuclei wh h were undergoing change preliminary to phagocyto- si during L E. cell formation and the inclusion bodies of L E. cells fluoresced brilliantly There was no similar fluorescence of the nucleus of the phagocytic cell or of any nuclei in

tachycardia pleurisy pericarditis and nephritis with nephrotic traits lymphadenopathy and psychic alterations (lack of interest apathy in one patient exacerbation of existing schizophrenia occurred) *Hematoserologic* findings revealed *considerably* elevated erythrocyte *sedimentation* rate hypergammaglobulinemia with hypoalbuminemia positive L E. cell phenomenon and leukopenia with shift to the left of neutrophils and anemia.

Of the above described clinical symptoms which together may be called the L E. cell positive syndrome " only ? were regularly observed viz., fever and general asthenia. The only significant specific and common hematoserologic finding was the positive L E cell phenomenon. Elevated erythrocyte *sedimentation* rate and *hypergammaglobulinemia* may occur in other *conditions* too

Generally the L.E cell positive syndrome is identified with Libman Sacks syndrome and acute disseminated lupus erythematosus Whether Libman Sacks *syndrome* may occur *without the L.E. cell phenomenon cannot be stated* as no such observations have been reported Under strict observation of all morphologic and serologic criteria the L.E. cell phenomenon is specific of the above syndrome and of high diagnostic value Therefore L.E. cell testing is recommended for *all diagnostically obscure* febrile *conditions* with progressive *general asthenia* elevated erythrocyte sedimentation rate and shift to the left of neutrophils in the hemogram.

► [The important question is whether the positive L.E. cell phenomenon by itself without other supporting evidence (increased erythrocyte sedimentation rate, hypergammaglobulinemia, fever asthenia, etc.) *is absolutely specific for systemic lupus erythematosus* The answer to this question, of course, depends on the criteria and test method used. No matter whether one believes that a positive L.E. cell phenomenon is 100% specific for and diagnostic of lupus erythematosus or not, the fact remains that the L.E. cell phenomenon is one of the major diagnostic advances of recent years. —Eds.]

Affinity between *Lupus Erythematosus* **Serum** *Factor* **and Cell Nuclei and Nucleoprotein** was demonstrated by Halsted R. Holman and Henry G Kunkel[7] (Rockefeller Inst) Starch zone electrophoresis of highly active L E. serum confirmed the finding of others that the factor migrates with the faster portion of the gamma globulin Nuclei from calf thymocytes rabbit *polymorphonuclear leukocytes and* human monocytes were prepared in sucrose calcium *solution* When

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each type was incubated in highly positive L.E. serums at temperatures between 18 and 38 C. and the nuclei then removed by centrifugation, the serums lost completely their ability to induce L.E. cell formation. Electrophoretic and immunologic determination of total serum gamma globulin before and after absorption with nuclei showed little change.

Adherence of the serum factor to the nuclei is suggested by the fact that nuclei which had been removed from L.E. serum, washed with cold saline until the solution was free from protein and then incubated with fresh human white blood cells were readily phagocytized to form L.E. cells. Nuclei exposed to normal serum and treated in an identical manner were not similarly phagocytized.

In an effort to determine the reactive component of the nuclei, similar experiments were done with isolated nuclear nucleoprotein. After absorption with the nucleoprotein, L.E. serum was unable to induce L.E. cell formation. When the nucleoprotein, after incubation with L.E. serum, was washed and incubated with fresh white blood cells strands of nucleoprotein were phagocytized by the white blood cells to form inclusion bodies very similar to those of the L.E. cells.

After treatment with desoxyribonuclease sufficient to remove about 50% of the desoxyribonucleic acid (DNA) the nuclei would absorb some of the L.E. factor and would readily release all of that absorbed on subsequent incubation at 56 C. If all the DNA was removed, none of the factor could be absorbed.

Exposure of nuclei to normal serum, to cirrhotic serum with very high gamma globulin and to serum with large amounts of euglobulin did not make the nuclei susceptible to phagocytosis nor did it interfere with their ability to absorb L.E. factor. However absorption of factor was prevented by prior treatment of nuclei with protamine, which is thought to bind the phosphate groups of DNA and with Atabrine.

Slides containing L.E. cells were reacted with fluorescent rabbit antiserum to normal human gamma globulin. Nuclei which were undergoing change preliminary to phagocytosis during L.E. cell formation and the inclusion bodies of L.E. cells fluoresced brilliantly. There was no similar fluorescence of the nucleus of the phagocytic cell or of any nuclei in

tachycardia pleurisy pericarditis and nephritis with nephrotic traits lymphadenopathy and psychic alterations (lack of interest apathy in one patient exacerbation of existing schizophrenia occurred) Hematoserologic findings revealed considerably elevated erythrocyte sedimentation rate hypergammaglobulinemia, with hypoalbuminemia positive L.E cell phenomenon and leukopenia, with shift to the left of neutrophils and anemia.

Of the above described clinical symptoms which together may be called the L.E. cell positive syndrome, only 2 were regularly observed, viz. fever and general asthenia. The only significant specific and common hematoserologic finding was the positive L.E. cell phenomenon. Elevated erythrocyte sedimentation rate and hypergammaglobulinemia may occur in other conditions too

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(7) Science 126 162-163, July 26, 1957

esce brightly when a buffy-coat preparation pretreated with L E. positive serum was stained with fluorescent conjugate.

The results show the presence in the L.E. positive serums xammed of a factor with an affinity for tissue-cell nuclei Previous work has shown that a gamma globulin fraction is responsible for the L.E. cell phenomenon a part of which in ol es alteration of the nuclear material of white blood cells. This suggests that the L.E. cell factor is of an antibody nature, and the present demonstration in tissue cell nuclei of a fixed globulin derived from L.E. positive serum adds support to this hypothesis

Serodiagnosis with Antigens of Treponema Pallidum in Lupus Erythematosus. Detection of system c lupus erythem tosus has been greatly enhanced by laboratory aids chiefly the L.E phenomenon and the b ologic false positive (BFP) reactions With the ewer treponemal tests the T pallidum complement fixation (TPCF) the T pallidum immune adherenc (TPIA) and the T pallidum agglutination (TPA) tests, the d tection of BFP reactions has been made easier These tests are highly pecific, technically s mple to perform d relat ely nexpens e They have obvious advantages er the T pallidum immobilization (TPI) procedure in that killed treponemes o extracts thereof are used as anti gens, which may be tored under refrigeration and be made a ilable to smaller serologic laboratories without dequate facil ties to cope with the technically more complicated TPI test Although the pla e of BFP reaction, as related to vari u disease processes, is till undetermined, ts frequent oc urren e in acut disseminated lupus erythematosus has been established.

Charles R. Rein, Louis Chargin and Louise C Kelcec* (New York) studied 79 patient with proved lupu erythem tosu by serologic examin tions and variou serodiagnostic procedures Each specimen was examined with the Maz in VDRL, Kline e clus on and Rein-Bossak m croflocculat on tests nd cardiolipin complement fixation procedure. The pecimens also were tested with the TPIA and TPCF procedures, and in some in tan es with th TPI Included wer 46 patient with chronic discoid and 33 with systemic lupu erythematosus. Pos tive serologic tests for syphilis w th one or more of the test used were obtained in 35 pa

(*) A M A Arch. Dermat 75 230 235 February 1957

control preparations made with normal serum. Thus the localization of gamma globulin presumably L.E. factor on the affected nuclei during in vitro L.E. cell formation could be demonstrated.

These data suggest that the L.E. serum factor has an affinity for nuclear nucleoprotein and that DNA is involved in the bond. The fact that the L.E. serum factor is a gamma globulin that appears to react with antiserum to normal gamma globulin suggests that the factor may be an antibody.

[An important fact revealed in these studies is that Atabrine® prevented absorption of the L.E. factor by the nuclei. Perhaps this effect of Atabrine is the basis of the beneficial therapeutic action of this and other antimalarial drugs, at least in the systemic form of lupus erythematosus.

In subsequent work Robbins and associates (Proc. Soc. Exper. Biol. & Med. 96:575, 1957) found that serums from patients with active lupus erythematosus fixed complement with a wide variety of nuclei from different organs and species. In most instances complement fixation occurred in roughly parallel titer with both nuclei and DNA. Cross absorption experiments suggested that there are two distinct factors, viz., the L.E. factor which appears to be related to the factor responsible for complement fixation with nuclei and another distinct factor which is responsible for complement fixation with DNA. The independent behavior of the complement fixation with DNA was unexpected.—Eds.]

Serum Factor in Lupus Erythematosus with Affinity for Tissue Nuclei was demonstrated by E. J. Holborow, D. M. Weir and G. D. Johnson.[8] Tissue and cell preparations were treated with anti human globulin serums conjugated with fluorescein isocyanate and examined microscopically with an ultraviolet light source. Two rabbit anti human globulin serums were used. One was prepared in rabbits injected intravenously with their own red cells previously agglutinated by pooled human serum. The other was Coombs anti human globulin serum. Tissues examined were skin, heart muscle, kidney, thyroid and spleen.

In all tissues examined, exposure of the section to L.E. positive serums resulted in marked specific fluorescence of the nuclei on subsequent staining with the antiglobulin conjugate. This was never noted when normal serums were used to treat the section. The specificity of staining by the antiglobulin conjugate was confirmed by showing that its ability to stain tissue treated with L.E. positive serum was blocked by pretreatment with unconjugated antiglobulin serum but not by normal serum. Both rabbit anti human globulin serums gave similar results, varying only in intensity of fluorescence. White blood cell nuclei were found to fluo-

(8) Brit. M. J. 2:732-734, Sept. 28, 1957.

However the high percentage of some abnormal labora t ry findings in patients with BFP reactions offers additional ev dence that the reaction must be given serious considera tion. A third of patients with BFP reactions with no appar ent clinical illnes had one or more positive laboratory find ings indicative of bnormal globulins. Diagnosis of BFP reaction requires careful history taking and physical exam ination fo vague signs and symptoms, especially in young women. A minimal laboratory examination should include complete blood cell counts determination of sedimentation rate, cephalin flocculation and thymol turbidity tests and protein partition. If these tests and history and physical ex amination are normal, the patient may be observed yearly with instructions to return earlier if symptoms appear If the tests are positive more careful and frequent observation is indicated.

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Leukocyte Agglutinins in Collagen Disease. Sven-Åge Killmann[3] (Copenhagen) found leukocyte isoagglutinins in 18 of 40 patients with collagen diseases (rheumatoid arthri t s, systemic lupus erythematosus, scleroderma, Felty s syn drome and other collagen diseases) Leukocyte agglutinins occurred oftenest in systemic lupus erythematosus, being present in 9 of 12 patients with this disorder A relation was found between occurrence of leukocyte agglutinins and pre- ious blood transfusions but no relation between leukocyte agglutinins and previous pregnancies was demonstrable. At least 4 and probably more of the leukocyte agglutinins found in this study could not be attributed to isoimmuniza tion as the pat ents had not eceived transfusion or been pregnant.

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In 4 patients the BFP reactions were present for 1-4 years before recognizable clinical manifestations of lupus erythematosus appeared. Prolonged periodic observation of the chronic BFP reactor is a necessity and may lead to early diagnosis of systemic lupus erythematosus.

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Studies on Significance of Biologic False Positive Reaction. The Treponema pallidum immobilization test, a specific means of diagnosing the biologic false positive reactor separates syphilitic from nonsyphilitic patients within minor limitations. However, the diagnosis of biologic false-positive reactor raises significant questions concerning the patient with this finding. Of 555 patients with biologic false-positive reactions (BFP) studied by J. Lowry Miller, Marvin Brodey and Justina H. Hill[1] (Columbia Univ.), 21.6% had systemic disease in one form or another, 2% having systemic lupus erythematosus. If all patients with rheumatoid arthritis, anemias, vague symptoms and neurologic signs are included, an additional 13% could loosely be classified as having lupus erythematosus diathesis. The rest of the patients with systemic disease had diseases often to be anticipated in their particular age group and not apparently influenced by the factors causing the BFP reaction.

Females accounted for 71% of the patients with BFP reactions and 84% of those with systemic disease. The known onset of the BFP reaction reached highest incidence in persons aged 20-30. The BFP reaction was persistent (known to be present over 6 months) in 254 patients. In the group with systemic disease the reaction had been present 1-40 years, with a mean duration of 4 years. In the group without systemic disease the period of known duration of the positive reaction varied from 6 months to 31 years, with a mean of 2 years. There are enough patients with known long duration of the positive reaction to suggest that the phenomenon may be borne with no apparent detrimental effect in a sizeable group of patients.

(1) J.A.M.A. 164:1461-1465, July 27, 1957.

However the high percentage of some abnormal laboratory findings in patients with BFP reactions offers additional evidence that the reaction must be given serious consideration. A third of patients with BFP reactions with no apparent clinical illness had one or more positive laboratory findings indicative of abnormal globulins. Diagnosis of BFP reaction requires careful history taking and physical examination for vague signs and symptoms, especially in young women. A minimal laboratory examination should include complete blood cell counts, determination of sedimentation rate, cephalin flocculation and thymol turbidity tests and protein partition. If these tests and history and physical examination are normal, the patient may be observed yearly with instructions to return earlier if symptoms appear. If the tests are positive more careful and frequent observation is indicated.

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glutination also occurred in saline dilutions having a lower concentration of gamma globulin than normal serums.

Type specificity of the leukocyte agglutinins could not be demonstrated. The agglutinins were unrelated to red cell antibodies and to the L.E. factor. In the present group the agglutinins did not appear to be associated with leukopenia. However, this lack of correlation between presence of leukocyte agglutinins and leukopenia does not rule out leukocyte agglutinins as a cause of leukopenia in some patients with collagen disease. An agglutinin may be autoaggressive and shorten the life span of leukocytes without resulting leukopenia as long as the maximal rate of leukocyte production exceeds the rate of destruction.

Diagnosis of Lupus Erythematosus: Probable Significance of Pantothenate Blood Levels. Albert H. Slepyan (Highland Park, Ill.), D. V. Frost, L. K. Overby, R. L. Fredrickson and *Arnold E. Osterberg*[3] *(North Chicago, Ill.) found the ratio* of bound to free pantothenic acid levels of the whole blood of normal persons to be reasonably constant, whereas blood from lupus erythematosus patients showed a strikingly low ratio. The mean ratio of bound to free pantothenic acid in 20 normal persons was 4.3 (range 2.4-7.5). For 10 patients with systemic lupus erythematosus the mean ratio was 1.4 (range 0.2-2.9) and for 11 with discoid lupus erythematosus the mean ratio was 1.9 (range 0.6 to 3.6).

All ratios for lupus erythematosus blood were lower than the mean ratio of normals and only 3 were higher than the lower range of normals. Regardless of the severity of lupus erythematosus or presence of L.E. cells, the ratio remained persistently low. These findings substantiate the belief that discoid and systemic lupus erythematosus are one and the same disease *and suggest the same enzymatic defect as being* present in both stages of the disorder.

Patients with manifestations of the lymphoblastoma group show abnormally low bound-free ratios, suggesting that here too the same inherent enzymatic error *underlies both* processes. It is interesting that a high bound-free ratio was found in 3 patients with lymphocytic infiltration of the skin. This disorder is frequently confused clinically and histopathologically with lupus erythematosus and the lymphoblastoma group. Should further studies prove this ratio to

(3) A.M.A. Arch. Dermat. 75:845-850, June 1957.

be constant, a helpful procedure will be available in differential diagnosis.

Study of specimens from 15 patients with polymorphous light eruption showed no constant bound-free ratio in this disorder.

► [If these findings are confirmed in further studies, another laboratory aid for diagnosis of lupus erythematosus will become available. It is noteworthy that this method does not differentiate between chronic discoid and acute disseminated forms of the disease.—Eds.]

Systemic Involvement in Chronic Lupus Erythematosus. William Kushniruk[4] (Saskatoon, Sask.) studied 35 patients (15 men and 20 women) with chronic lupus erythematosus as extensively as patients with frank systemic forms of the disease are usually studied. Features sought were those generally accepted as occurring in the systemic disease. Thirty patients had typical chronic discoid lesions and 5 had typical chronic disseminated lesions. Average duration of lesions was 9.9 years. All were thought to have uncomplicated cutaneous forms of lupus erythematosus without any systemic manifestation.

Temperatures of 99-100 F. were consistently present in 13 patients with chronic discoid and in 4 with chronic disseminated lupus erythematosus. No foci of infection were found to explain the fever. Malaise with loss of energy was present in 17 patients in the discoid group and in 4 in the chronic disseminated group. Ten patients with chronic discoid lesions lost weight after the lesions appeared.

Migratory joint pains involving the hands, wrists, knees and elbows were described by 10 patients. Radiologic examination of the joints was negative. Eight patients had photophobia, 7 had blurred vision and 2 had diplopia. Fundi were normal in all 35 patients, but in 3 in the chronic discoid group corneal ulcer, an old iritis and a healed keratitis were found.

No patient had pleuritic pains at the time of examination, but 3 had a history of repeated attacks of pleurisy. Five others had chronic productive cough. Physical examination of the lungs was negative in all, but radiologic chest examination revealed healed tuberculous complexes in 8 patients, increased bronchovascular markings in 4, bilateral pleural thickening in 4, minimal pleural effusion in 1 and pulmonary fibrosis in 3. In the chronic discoid group 8 patients had ex-

[4] [illegible] M. A. J. 76 184-192, Feb. 1, [illegible]57.

ertional dyspnea and 2 exertional precordial pain. Five had apical systolic murmurs. X ray study showed left-sided heart enlargement in 3 patients There were no cardiovascular symptoms in the chronic disseminated group Persistent hypertension was noted in 1 patient with chronic disseminated lesions and in 5 with chronic discoid lesions. Electrocardiograms were negative in all but 1 chronic discoid patient

Raynaud s phenomenon was present in 6 patients hepatomegaly in 8 and splenomegaly in 1 Five patients had anorexia 2 nausea and vomiting 2 diarrhea and 2 obstinate constipation. Four patients menstruated irregularly 2 had dysmenorrhea and 1 menorrhagia Initial chronic discoid lesions occurred during pregnancy in 2 patients Five patients with chronic discoid lesions had multiple pregnancies after appearance of the lesions 3 noted no change in the lesions and 2 noted improvement during pregnancy One with chronic disseminated lesions also noted improvement during pregnancy

Neurologic complaints were observed only in the chronic discoid group Six patients had headaches and 2 had vertigo. Two patients had numbness in facial areas and 11 had paresthesias in the extremities Superficial reflexes were normal in all 35 patients Four had psychiatric symptoms and 1 had epilepsy

Lymphadenopathy was noted in 18 patients. Sedimentation rates were determined in 26 chronic discoid cases and in 5 chronic disseminated cases In discoid cases the rate was normal in 3 slightly increased in 2, moderately increased in 13 and rapid in 8 In chronic disseminated cases the rate was slightly increased in 2 moderately increased in 2 and rapid in 1 No biologic false positive reaction for syphilis was observed The L.E cell phenomenon was negative in 25 patients so examined but tart cells were noted in preparations from 2 patients with discoid lesions. Seven patients had white blood cell count of less than 4 000 and 13 others had counts below 5 000 Differential examinations showed lymphocytosis in 16 chronic discoid and in 5 chronic disseminated cases. Anemia was present in 9 patients

The urine was abnormal in 18 patients 10 had albuminuria 17 had white blood cells 9 had red blood cells and 8 had casts in the urine Total serum protein was elevated in 3 patients

Reversal of the albumin-globulin ratio was observed in 15 patients with discoid and in 3 with disseminated lesions. Elevation of the gamma globulin fraction was noted in 8 of 14 patients so examined. Urinary coproporphyrin excretion was significantly increased in 4 patients. Cerebrospinal fluid was normal in 5 patients examined. In 1 with chronic discoid lesions the bone marrow was hypoplastic with neutropenia. Examination in 5 other patients was negative.

According to Kushniruk, the abnormalities encountered in these patients were similar to or identical with those found in subacute and acute lupus erythematosus but were much less severe. It would appear that presence of these abnormalities was more than coincidental because they were found in patients thought to be free of systemic involvement. They indicate that organs and systems other than the skin are involved in chronic lupus erythematosus, and that chronic, subacute and acute lupus erythematosus are in all probability variants of the same disease.

► [Results of this comprehensive search for signs of systemic abnormalities in patients who clinically presented the chronic discoid form of lupus erythematosus add to the evidence that chronic, subacute and acute lupus erythematosus may be variants of the same disease. The editors are of the opinion that the many data favoring this viewpoint should prompt every physician to rule out the other forms of lupus erythematosus when undertaking management of what is clinically the chronic discoid form of the disease.

It is interesting that in Kushniruk's group of patients the L.E. cell phenomenon was negative and there was no biologic false positive serologic reaction. The absence of positive reaction to these particular serologic tests, however, in this series of patients does not necessarily militate against the relationship between chronic and acute lupus erythematosus. —Eds.]

Lupus Erythematosus Syndrome. Relationship of Discoid (Cutaneous) Lupus Erythematosus to Systemic (Disseminated) Lupus Erythematosus was investigated by A. J. Reiches[4] (St. Louis) by means of a survey conducted among dermatologists and internists. Of 792 dermatologists who replied 600 had not noted transition of discoid lupus into the acute disseminated disease. However, 192 had observed 353 cases of chronic discoid lupus that were followed by the systemic disease. Systemic manifestations occurred from months to more than 10 years after appearance of the skin lesion. Of 100 internists who replied, 39 stated that there is a relationship between discoid and acute disseminated lupus erythematosus. Results of these surveys as well as previous-

[4] Ann. Int. Med. 46:678-683, April, 1957.

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when more than one site was involved, lupus erythematosus was observed first on other parts and subsequently it appeared at a site of trauma. In at least 18 cases the lesions of discoid lupus erythematosus were of occupational origin.

The traumatizing agents reported were: in 31 cases, burns of different types; in 9, blows from various objects; in 11, lacerations; in 6, scars; in 3, vaccination scars; in 2, subcutaneous injection; in 3, x-radiation; in 2, tattoo; in 2, frostbite; in 1, gunshot wound; in 1, lip biting; chilblains (one correspondent reported this was responsible in many of his cases); in 1, cutaneous planing, and in 6, unspecified type of trauma.

Although it is recognized that the validity of some cases may be questioned, there appears to be adequate evidence that trauma occasionally is an important factor in determining the localization of lesions of chronic discoid lupus erythematosus. It is possible that in a person with predisposition to lupus erythematosus by virtue of a focus of infection, tissue sensitization due to earlier infections or some other obscure cause, trauma may, by lowering tissue resistance, make the site of injury more susceptible to development of lesion.

► [The authors state that although sunlight should be included as a traumatizing agent, they were interested primarily in other types of trauma. For this reason, 6 cases of lupus erythematosus appearing after sunlight exposure were not included in their tabulations. Although we appreciate why they did not wish to include sunlight as a traumatizing agent, we would like to call attention to x-rays, another form of irradiation, which was reported as the traumatizing agent in 3 of their cases. This brings up the question of whether rays of the sun cause flare-up of lupus erythematosus through some specific mechanism or simply by "burning" susceptible terrain in susceptible patients.—Eds.]

Chronic Lupus Erythematosus of Conjunctiva is reported in 2 cases by X. Vilanova, C. Cardenal and J. M. Capdevila (Univ. of Barcelona).

Case 1.—Woman, 30, with erythematous lesions of chronic lupus erythematosus for 4 years, on examination showed characteristic lupus erythematosus plaques, with erythema, hyperkeratosis, plugging of follicles and slight central atrophy on the ears, behind the left ear and, without hyperkeratosis and atrophy, on the dorsum nasi. On both lips there were numerous red to bluish red lesions, which were ill-defined toward the mucosa and showed a slightly raised, whitish, scaly, infiltrated edge next to the cutaneous part of the lip. The surface of the vermilion border was dry and scaly and often cracked and bled. The buccal mucosa of the right cheek showed an erythematous, ruby plaque with whitish, occasionally exfoliating surface.

The ocular lesions were the typical pea-sized plaques of chronic

Dermatologica 113:[illegible]-231, October [illegible].

ly described similarities in hematologic vascular biochemical and microscopic pathology of the skin in these conditions strongly suggest that discoid and systemic lupus erythematosus are stages of the same disease entity Reches suggests that clinically the syndrome may be divided into (1) a localized discoid (cutaneous) phase which generally is benign and (2) a systemic (disseminated) phase which may or may not be associated with skin lesions. Use of the terms discoid (cutaneous) phase of lupus erythematosus and systemic (disseminated) phase of lupus erythematosus is suggested. It is apparent that the discoid (cutaneous) phase when existing alone may in some cases develop into the systemic type.

Three cases are reported in which discoid lupus erythematosus of 6 10 and 13 years duration developed into the systemic form of the disease

► [The fact that 600 dermatologists questioned by Reches had not noted a transition from chronic discoid to acute disseminated lupus erythematosus speaks for itself. On the other hand, one cannot overlook the replies from 192 dermatologists who observed 353 cases of chronic discoid lupus erythematosus that were followed by the acute disseminated form. This difference in observations could be the result of different criteria for diagnosis used by the various dermatologists. There are certain clinical pictures that may be diagnosed as chronic discoid lupus erythematosus by some and as subacute disseminated lupus erythematosus by others. This holds true particularly for cases of widespread chronic discoid lupus erythematosus.

Even using the most modern laboratory procedures, no hard and fast criteria have been set up that must be satisfied to make diagnosis of one or the other form of this disease. We agree with Reches that the chronic discoid form in all probability is only one phase of the disease but since in some cases there is evidence of systemic involvement, minor as it may be, we do not favor the use of "cutaneous" and "systemic" to differentiate between the chronic and acute forms. The final answer as to the relationship of these conditions is yet to be found and is likely to come from the laboratory rather than from the clinician.—Eds]

Discoid Lupus Erythematosus Following Trauma Report of Cases and Analysis of Questionnaire Occasional reports of lupus erythematosus developing at sites of trauma have appeared in the literature. Arthur B Kern and Bencel L Schiff[6] (Boston Univ) report 5 such cases They sent a questionnaire concerning incidence of trauma as a factor in the pathogenesis of discoid lupus erythematosus to many dermatologists Of 266 who replied 212 stated they had not observed this relationship whereas 54 reported they had observed a total of 78 cases In about half the cases the traumatized site was the only one involved In most cases

(6) A.M.A. Arch. Derm 75 :685-688 M 1957

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Dermatologica 113 226-231, October 1956.

lupus erythematosus with erythema, hyperkeratosis, plugging of follicles and slight atrophy extending from the right inner corner onto the right lower eyelid, ending at the external corner The ciliary margin was erythematous, thickened, slightly everted (Fig 7) The conjunctiva of the upper and lower right eyelid showed small, markedly erythematous, less elastic and slightly depressed areas (beginning atrophy) Histologic study of the ocular lesions revealed thin mucosal epithelium destruction of the basal cell layer mostly by infiltration, loss of normal arrangement of the prickle cells and mild lymphoid and polynuclear exocytosis (Fig 8) In the papillary layer and in the



Fig. 7 (top left) —Ocular manifestations of chronic lupus erythematosus in Case 1
Fig 8 (right) —Histologic appearance of conjunctival lesion
Fig 9 (bottom left) —Ocular manifestation in Case 2
(Courtesy of Vilanova, X et al Dermatologica 113 226-231 October 1956.)

superficial corium there were dense mono-nuclear infiltrates consisting mainly of lymphocytic-histiocytic cells and scanty polymorphonuclears and plasma cells. There was interfascicular edema. Collagen and elastic fibers were missing within the infiltrates. In some areas of the corium where no infiltrate was noted, fibroblastic proliferation was evident. The capillaries were dilated, and some vessels showed perivascular infiltration

Although treatment with chloroquine (0.25 Gm./day) was irregular because of negligence of the patient and occurrence of erythropenia, it was always effective. After 10.5 Gm. the lesions almost completely disappeared and redness of conjunctiva was less marked. Recurrence appeared on the lower eyelid and lips after 2 weeks, and again the lips healed. Ocular lesions finally consisted of only well defined erythema of the conjunctiva and pointlike erythema of the cutaneous part of the eyelid

CASE 2.—Woman 23 showed slightly atrophic scaly plaques of the

scalp without alopecia and characteristic chronic lupus erythematosus of the face, presternal region and shoulders. The oral mucosa was free. Ocular lesions (Fig 9) corresponded to those of Case 1, the cutaneous lesions of the eyelids showing little infiltration, rosy color slight scaliness, papular border and slightly depressed, nonatrophic center Conjunctiva of the lower eyelid showed well-defined erythema, slightly granular surface infiltration and vasodilatation which extended onto the lateral corner and upper eyelid.

Clinically chronic lupus erythematosus of the conjunctiva is not different from cutaneous and mucosal lesions. Coexistence with these manifestations and therapeutic response permit the clinical diagnosis of lupus erythematosus conjunctivae

Deep Nodular Lesions Appearing during Course of Fatal Acute Lupus Erythematosus. Without discussing the problem of lupus erythematosus profundus (Irgang Kaposi) X Vilanova and J Pinol (Barcelona) state that the appearance of nodular lesions during the course of acute lupus erythematosus, as in the case reported by Milner in 1953 is exceptional. In the subacute forms of the disease such lesions were first noted by Kaposi recently they have been described again by Ramos e Silva and Portugal. In all these observations, the symptomatology of the nodules was dissimilar but from the authors findings in the case reported, the dissimilarity was not fundamental but rather the result of the stage of evolution of the lesions and treatment to which they had previously been subjected. In the patient described, a biopsy specimen was obtained from a nodule of 4 day duration, which made it possible to describe the heretofore unknown initial histologic lesions of this rare eruption

Housewife 44 first became ill 3 years before examination with what appeared to be rheumatoid condition, manifested by joint pains unaccompanied by swelling but with obvious functional incapacity and slight edema of the legs at night. These symptoms disappeared in few days, but recurred with increasing severity and for longer periods during the succeeding winters. Treatment with antalgic drugs failed to produce any significant improvement. Finally 60 days before admission in June 1955 she had dysuria and pollakiuria lasting month At the same time the edema of the feet increased and failed to disappear with rest. A few days later she had oliguria followed by anuria for 48 hours and a temperature of 100 4 F A mercurial diuretic was given and diuresis of 6 L./24 hours followed Shortly thereafter round erythematous spots appeared on the lower limbs, later spreading to the backs of the hands and face An episode

Ann dermat et syph 84 37-44, Jan Feb [illegible]

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of pleuropneumonia with dyspnea and pain on the left side occurred a month before she was first seen. This lasted about 3 weeks despite treatment with penicillin and later hydrazide. Meanwhile, the skin symptoms, consisting now of reddish patches, urticarial plaques and bullous lesions, persisted and spread over the chest and back. The patient's general condition on admission was poor. She was treated with analeptics, cardiotonics and cortisone acetate, and although the temperature which had reached 104 F declined rapidly and all the skin lesions receded there was no improvement in the general condition and after a few days diffuse joint pains reappeared. Further treatment was ineffectual and in September 1955 the patient died of asystole.

The most significant and unusual feature of this case was the appearance on two occasions of nodular formations that were dermohypodermic in location. They were cherry to walnut sized, elastic in consistency and covered with skin of a normal appearance but with a color ranging from dark red to pale pink. On the first occasion the nodules disappeared spontaneously and on the second they responded rapidly to cortisone disappearing within 48 hours. Histologic examination of a 4-day-old nodule showed edema and fibroblastic proliferation in the corium fibrinoid degeneration and perivascular infiltration with histiomononuclears and a few polynuclear leukocytes in pyknosis. The inflammatory process extended to the hypoderm with a tendency toward reinforcement and with hyaline degeneration of the interlobular connective tissue bundles. Although on superficial consideration, the histologic structure of the nodules in this case may seem unlike that of the nodules described by Milner, Ramos e Silva and Portugal the resemblances are more significant than the differences. Thus the dermic and hypodermic infiltration visible in the sections might by subsequent reinforcement become the extensive infiltrative nuclei described by Milner and the fibroblastic degeneration and tendency toward hyalinization might serve as the framework for the connective tissue changes predominating in the case of Ramos e Silva and Portugal.

Lupus Erythematosus Profundus (Lupus Erythematosus with Formation of Subcutaneous Nodules) In reporting 2 cases and reviewing the literature Delia Walther[9] (Univ of Frankfurt) states that the term lupus erythematosus profundus refers to cases of chronic lupus erythematosus during the course of which preceding following or concurrent with cutaneous manifestations of the disease subcutaneous swell

(9) Arch. klin. u. exper. Dermat. 204 183-204 1957

ngs and nodules appear which are soft to cartilaginous in consistency slightly or not tender and mobile on underlying tissues. The covering skin is of normal or livid red color and may show horny plugs, scaliness and changes typical of lupus erythematosus. The subcutaneous nodules, which are usually localized on the forehead, cheeks, chin extensor surface of the upper arms, buttocks and th ghs and less often on the scalp back, forearms and legs may clear completely or lea e deep depressions, even causing skeletization

Differential diagnosis must consider leukemic infiltrates lymphocytoma, Spiegler Fendt, Boeck Besnier Schaumann and Darier Roussy sarcoids, Bazin s disease and nonsuppurati e, hron panniculitis Diagnosis of lupus erythema tosus profundus may occasionally be extremely difficult and even impossible, e.g if deep nodular but nontypical lupus erythematosus lesions exist or f in the healing stage of the disease deep hollow like depressions have formed but rem na ts or typical scars of hronic lupus erythematosus are missing

The hist logic changes observed in lupus erythematosus prof ndus can be divided into two groups. The first showed chron c inflammatory infiltration in the deepest cutis and subcutis. In the mildest cases there were round cell infil trates n the deep cutis and subcuti w th plasma cells and fibrocytes, vasodilatat on with polymorphonuclears pyk notic nuclei a few foam cells giant cells, and, rarely epi thelioids, d cating an acute character of the pathologic proces From these findings the diagnosis of lupus ery thematos s profundus bviously cannot be made In the sec ond group which also includes h stologic findings in the ? cases reported by th author homogenization swelling fibrinoid or m coid degeneration of collagen, perivasculitis v sculitis, infiltration fibrinoid degeneration of vascular walls endoth lial swelling and degeneration and even obli teration of the vascula lumen are recorded gain and again Extensiv necrotizing nfl mmation of the adipose and collagen tissues were lso found, although not in all cases.

Findings of th kind were observed in extremely rare cases of cl ronic l pus erythematosus but are rather consistent with ascular and collagen changes in acute and subcut disseminated lupus erythematosus. E ery case of the d sease with subcutaneou nod les, particularly if histologic

changes reveal not only deep chronic inflammatory infiltrates but also marked collagen and vascular alteration should therefore be thoroughly observed and examined to find any signs of systematization or acute or subacute exacerbation of chronic lupus erythematosus e.g temporary rise in temperature arthralgia Raynaud s syndrome, pleurisy particularly leukopenia elevated erythrocyte sedimentation rate hyperglobulinemia and pathologic flocculation reactions

Subcutaneous nodules observed first by Kaposi (1869 and 1872) in cases of acute and subacute disseminated lupus erythematosus may also occur in chronic lupus erythematosus The author's own observations showed that the subcutaneous infiltrates appear occasionally without concomitant typical skin manifestations of lupus erythematosus that the face extensor surfaces of the upper arms and the gluteal or iliac region are usually involved and that there is good response to the various drugs effective in lupus erythematosus. Definite clinical diagnosis is only possible in patients with concurrent typical cutaneous manifestations of the disease and identical therapeutic response (healing recurrence deterioration) Histologic findings of subcutaneous infiltrates (above) do not warrant a definite diagnosis of lupus erythematosus but permit the exclusion of some diseases like sarcoidosis, Bazin s disease etc. The histologic diagnosis may be less difficult when changes exist in the middle and upper cutis which suggest lupus erythematosus When extensive proliferative or degenerative vascular changes and alterations of the collagen exist acute or subacute exacerbation of lupus erythematosus may be suspected but in that event clinical signs are likely to be present as well.

Dermatomyositis N G B McLetchie and N B Coward[1] (Halifax) describe observations in 8 children aged 1/2 13 Two died and 1 is crippled. The others recovered completely including 1 who had a relapse. Onset was insidious in 6 patients In 1 the initial symptom was an erythema that first appeared during treatment of a stomatitis with sulfonamides and mouthwashes In 1 patient increasing weakness followed an acute febrile illness necessitating 5 days in bed Muscular weakness was conspicuous in 6 patient mild in 1 and difficult to assess in 1 an infant aged 1 Weakness

(1) Canad M.A.J 76 1018-1029 June 15 1957

in ol ed the legs in all and variously also the arms, shoulder girdle and neck The weakness usually was first noticed as difficulty slowness or awkwardness in walking or climbing stairs.

In 4 *patients*, a *skin eruption* was the first sign noticed by the mother The skin eruption was present in one form or another in all. Rashes varied from bright red to dusky red nd even blue macular to blotchy to confluent. Distribution was variable and involved the face trunk and extremities A eruption was more common about the eyes and on the f rehead than at any other site. Nonpitting thickening of the skin was noted in 6 patients. In 2, scanty widely distributed, subcutaneous nodules were present both showed no lin cal edema, and erythema was confined strictly to the k n overlying the nodules. Two patients had bluish nodules in the tongue a d ins de the cheeks. One had swollen joints Generalized tenderness was not an outstanding feature although attempts to extend the legs were painful in 1 patient. All had low-grade intermittent fever but temperature of 103 F or more was noted in only 1 patient The sedimentation rate wa elevated in 7 of the 8 patients. Mild anemia wa ommon but leukocytosi and eosinophilia were not observed Lymphadenopathy was present in 6 patients but not conspicuously

One patient recovered without drug therapy Six received antibioti treatment and 3 were given cortisone. The authors feel the assumptson should be made, as in rheumatic fever that the disease is of an allergic nature, possibly streptococcic in origin and that prolonged antibiotic treatment may prevent ecrudescence. In all dental treatment was carried out as soon as the patient was fit Biopsy of the skin and muscle howed degeneration of muscle, vascul tis and, to a conspicuous degree fibrinoid necrosis of connective tissue. There was paucity of cellular response in the damaged tissue except in nodular lesions of the skin Lesions in the skin were deep in the dermis In addition to hyalin necrosis of muscle sa coly i was an outstanding feature

Dermatomyositis generally is held to be a rare condition but certain facts cast doubt on this (1) Children with severe lesion ca be restored to normal health and ther fore patient with mino cases probably recover frequently without pecial attention. (2) Biopsy is the only way to pos tively

identify the disease but many communications deny a specific pathology. In diagnosis by biopsy there must be much confusion from not recognizing fibrinoid necrosis as the hall mark of the disease. (3) Textbooks in general make little reference to the disease, and generally paint a horrific picture of remorseless progression to contracted ulcerated limbs which is erroneous. Accordingly the disease is probably more common than is generally recognized.

► [The increasing number of reports of dermatomyositis in children indicates a heightened awareness and interest by physicians in the disorder, improved methods of diagnosis, or less likely increased incidence of the disease.—Eds.]

Dermatomyositis: Review of 19 Cases in Adolescents and Children is presented by Mark Allen Everett and Arthur C. Curtis[2] (Univ. of Michigan). The initial symptom was facial erythema in 6 patients, fatigue in 4 and specific muscle weakness in 3. Six had miscellaneous findings. Physical findings during the course of the disease included grouped muscle weakness in 19 patients, fatigue in 18, periorbital erythema and edema in 17, extensor erythema in 16, muscle pain in 15, low-grade fever in 14, tissue induration and contracture in 12, poikiloderma in 11 and calcinosis in 8. Six patients had involvement of the muscles of deglutition with hypopharyngeal paralysis of varying degree demonstrable with barium swallows. Other than creatinuria, laboratory findings were not remarkable. None of the children had a malignant growth.

Eleven patients died, including 5 of the 6 with hypopharyngeal paralysis. Four died within the 1st year of hypopharyngeal paralysis and/or cardiac involvement. Those who died after the 1st year succumbed to infectious processes, chiefly pneumonia. Of the 8 survivors only 1 had detectable progression or activity after 3 years. Two patients who had severe calcinosis are partially active and 2 are confined to bed because of contractures and fibrosis of the extremities. Four patients are completely active and have only minimal-to-moderate fibrosis about some joints or insignificant residual pigmentary change.

Incidence of remissions and exacerbations was nil. Once the disease became inactive, it remained inactive. No therapy influenced the favorable outcome of the disease, although steroids in large doses tended to suppress indications

(2) A.M.A. Arch. Int. M. 100: 70-76, July, 1957.

of active inflammation and occasionally led to a feeling of well being. None had joint involvement or arthralgia at any time although ankylosis from periarticular fibrosis was not uncommon.

It would appear that dermatomyositis is a clinical entity that obtains its integrity from its unique clinical picture and rather typical course, eventuating in death, arrest or recovery usually in 3-36 months. Although the histopathologic features often are not diagnostic, the prominence of atrophy necrosis, homogenization and degeneration of skeletal muscle fibers is suggestive, particularly when accompanied by moderate inflammatory changes. Although the cause is not known, the authors feel that the documented series of dermatomyositis present enough similarity in onset, course, outcome and pathologic findings to call attention to and to protest vigorously the current trend toward broadening of the concept of dermatomyositis into a nebulous nonentity with a meaningless name.

► [It is notable that malignant tumors were not found in any of this group of very young patients, including the 6 who came to autopsy. A girl, 6, with dermatomyositis who recently was under our care showed a favorable response subjectively and objectively to therapy. Under treatment with daily administration of 5 mg. prednisone, 250 mg. chloroquine, 250 mg. ... and multiple ... there was distinct improvement of the fatigue, periorbital erythema and edema, extensor erythema, and the low grade fever.—Eds.]

Histologic Study of Muscle in Dermatomyositis and Similar Syndromes in 22 cases led P. Le Coulant and L. Texier[3] (Bordeaux, France) to take issue with those who wish to classify all musculocutaneous diseases in the same category. The other authorities are content to confirm the muscular lesion microscopically without considering the general anatomic evolution and systematization of the lesions chronologically and topographically. Thus, the possibility of histologic classification of various syndromes recognized clinically is delayed.

In dermatomyositis, edema is the primary lesion involving both interstitial and cellular elements; the fibers are swollen in irregular loops sometimes piled on each other. When cellular edema is predominant, the fibrils assume an undulated shape as if they were too narrowly confined in their sarcoplasmic sheath. Lesions vary greatly in different cases also with regard to their polymorphism in the same speci

(3) Ann. dermat. et syph. 84: 377-393, July-Aug., 1952.

men By studying the age of the pathologic process and its type of evolution a schedule of progression of histologic changes in the muscle can be established. In the subacute phase (biopsy 2 months after onset) there is merely parenchymatous edema. Sometimes minute and tedious examination is necessary to discover localized lesions in some fiber or fiber fragments conversely there may be massive disintegration of a whole bundle of fibers without any reaction in interstitial tissue In the advanced stages (3-6 months after onset) degeneration is more extensive and diffuse Muscular fibers are indicated by sarcolemmas and garlands of nuclei outlining their contour Two varieties of cellular reaction can be distinguished (1) proliferation of nuclei, segmentation of sarcoplasm and formation of macrophages encountered as circular blocks of Zenker degeneration and (2) appearance of discrete infiltrates in interstitial spaces. In the more advanced types known as poikilodermatomyositis the classic picture appears complete.

In scleroderma of either edematous or progressive type the dominant histologic element is interstitial consisting of dense lymphohistiocytic cellular plaques which dissociate and infiltrate bundles and fibers followed by collagenous deposits indicative of a progressive sclerosis. The parenchyma is involved only by encroachment of the infiltrate Sometimes isolated fibers escape degeneration but are surrounded by a collagenous mass.

In acute disseminated lupus erythematosus muscular biopsy sometimes is useful in doubtful cases clinically confused with dermatomyositis In an area of relatively pronounced edema interstitial reactions are predominant there is dilatation of vessels with slight thickening of their walls and perivascular infiltrate predominantly lymphocytic with perhaps slight fibrinoid degeneration in slightly proliferative collagenous tissue The parenchyma reacts secondarily on contact with primary lesions

In periarteritis nodosa the histologic picture is dominated by vascular lesions swollen arteries with thick walls and cellular infiltration sometimes with endarteritis and thrombosis and fibrinoid degeneration of collagen The infiltrate diffuses in more or less edematous interstitial tissue Lesion of muscular parenchyma are minimal edema, disappearance

of transverse striation and undulated fibrils in contact with vascular lesions

The three types of muscular lesions are distinguished as follows (1) in lupus erythematosus and periarteritis nodosa, the lesions are tied to the vascular element and appear logically to belong to pathologic allergies (2) scleroderma definitely is a part of what is called collagen disease and (3) conversely the histologic type of dermatomyositis centered primarily and preponderantly in the muscular parenchyma seems to direct investigations toward an autonomous muscular disease.

► [These observations regarding differences in the histologic changes between dermatomyositis and other collagen diseases appear to agree with those of O'Leary Lambert and Sayr (J Invest. Dermat. 24 301 1955) These authors besides doing histologic studies performed electromyographic tests. They noted that the electromyogram in dermatomyositis as similar to that of other myopathies in which active degeneration of muscle fibers without inflammation was found on histologic examination. Only few patients with acrosclerosis and systemic lupus erythematosus and none with scleredema showed similar electromyographic changes. Most patients with periarteritis nodosa had abnormal electromyograms of the type usually associated with neuritis.—Eds]

Dermatomyositis and Incidence of Associated Malignancy Onset of dermatomyositis is usually fairly acute, with heliotrope erythema, brawny edema of the face—particularly the eyelids—and muscular weakness. The edema and erythema may involve the extensor aspects of the extremities and later progress to a mottled scaling with firmness of the skin and atrophy The muscles may be so weak as to cause difficulty in swallowing or talking Muscular soreness may be present.

The usual laboratory findings are moderate leukocytosis with relative lymphopenia, alteration in the ECG due to muscle changes in the heart and occasionally albuminuria. Less common clinical features include a history of sun exposure before onset, serous effusions arthritic changes, Raynaud's syndrome and calcifications deep in the muscles. Fibrosis and atrophy of muscle are common, and the skin thickening that comes months after onset is not the hidebound type seen in scleroderma, but a brawny thickening suggestive of edema.

Charles Sheard Jr and Peter T Knoepfler[4] (Cornell Univ) report that of 14 patients with a definite diagnosis of dermatomyositis during 1935-54 6 had malignancy 2 had cancer

[4] A M A Arch Dermat 75 234-237 February 1957

of the breast 1 of the ovary and 3 of the intestinal tract. By comparison of 50 patients aged 50-60 who died of coronary thrombosis only 1 showed a hidden malignancy at autopsy The incidence of malignancy in white persons who die of all causes between ages 50 and 60 is 26% The incidence of malignancy associated with dermatomyositis is higher than could occur by chance or circumstance and these data, therefore, seem significant

Since a similar high incidence of malignancy has not been reported in scleroderma or other diseases difficult to differentiate from dermatomyositis it is important to recognize dermatomyositis early in its course After the diagnosis has been made particularly if the patient is an adult in the cancer age group and if there is a family history of cancer intensive measures must be taken to search out the cancer while it is operable

It cannot be said there is a cause and effect relation between dermatomyositis and malignancy since the two conditions appear to arise coincidentally in many patients. There might even be a common cause.

► [Although the series of Sheard and Knoepfler is small, it speaks strongly against the argument of a chance association between dermatomyositis and internal malignancy —Eds.]

Dermatomyositis Unusual Features Complications and Treatment of this relatively rare nonsuppurative polymyositis are reported by Herbert B Christianson Louis A. Brunsting and Harold A Perry[5] (Mayo Clinic and Found) in 179 females and 91 males (2 1 ratio) aged 2½ 72. Malignant disease noted in 18 (6.7%) patients was located in the breast (6) rectum and/or colon (4) cervix (2) lymph nodes of the neck (2) and prostate ovaries kidney and pituitary (1 each) The association of malignant disease with dermatomyositis was incidental the authors believe Clinical data suggest that malignant disease is associated with scleroderma, as well as with dermatomyositis and that there is an insignificant difference in the degree of association in respect to the two diseases

Two females had spontaneous primary (nonsteroid-induced) Cushing's syndrome and 2 had positive clot tests for lupus erythematosus A woman 36 and a man 64 had pityriasis rubra pilaris like eruptions of the palms and soles about 1 year before clinical evidence of dermatomyositis

(5) A.M.A Arch Dermat 4 581 589 December 1956.

Dy phagia was common and abdominal pain not infrequent. Other gastrointestinal manifestations were hemorrhage, perforation of the stomach and intra abdominal adhesions. Calcinosis occurred in 16 (29.1%) of 55 patients under age 16 and in 12 (5.5%) over age 16. Osteoporosis was present in 12 (21.8%) of patients under age 16 and in 18 (8.4%) of those aged 16 or older. There was no definite relation between calcinosis and osteoporosis though both occurred more often in the younger group.

Cortisone was gi en to 62 patients in doses of 100 mg/day for adults and 25-50 mg/day for children. Of 28 who mpro ed, 9 obtained permanent remission 15 were un m pro ed and 3 becam worse. Untoward effects of cortisone were hypertension in 3, diabetes n 3 osteoporosis in 5 n creased weaknes in 3 and de th in 1. The good results n th cort sone warrant its long-term use.

► [An informativ article with important, helpful clinical facts that should aid in diagnosis of this rather rare disease. The authors, contrary to the opinion of some, believe that the 6.7% incidence of malignancy associated ith dermatomyositis is coincidental and might be expected in the age group in hich dermatomyositis occurs. W suspect that incidence of malignancy associated ith dermatomyositis might be found to be greater if more intensive study for presence of internal malignancy were made in all patients ith dermatomyositis and if all cases in which this relation is found were reported.

W recently saw oman with dermatomyositis in hom extensive ork-up failed to reveal any evidence of existing internal carcinoma. In ... of progression of the disease, laparotomy performed and very early adenocarcinoma of both ovaries was found.—Ed.]

Periarteritis Nodosa as Skin Disease reported by Ingema Lindgren a d Curt Lundma k[4] (Sodersjukhuset Stockholm) Periarteriti nodosa present a aried and changi g clinical p ct re t may produc hanges in any organ of the body through its ffect on the blood essels. Cutaneous le ion occu n about 25% of the patients. In th eries of 14 th lesion ranged from pea-sized cutaneous and ubcuta neous nod les, with a vascula grouping to palm-sized in filtrates and lcerations. Les ons resembling erythema nodosum or erythema ind ratum wer often found. Also seen were lesion of l vedo racemosa, especially l vedo ret cularis. Skin ymptoms ranged from none to itch ng pricking sen sat on and local tenderness. General ymptoms ncluded fatigue malaise fever muscula tenderness and per pheral eurologic disturbances. An elevated sedimentation rate in creased eosinophils and a raised antistreptoly n titer oc

(4) Acta dermat venereol 36 343 356, 1956

curred frequently Histologic examination showed partial necrosis of the elastin sector shaped lacunae in the elastic lamina and marked inflammation of the arterial wall.

Periarteritis nodosa must be differentiated from other diseases with vasculitis In it characteristic arterial changes dominate whereas in erythema nodosum the change is in the connective tissue septa of the subcutaneous layer In erythema induratum there is subcutaneous necrosis and a pronounced tuberculoid structure.

Other than general care and rest in bed no specific treatment has been effective for periarteritis nodosa, although steroids antibiotics x ray therapy and antiallergic regimens have been attempted. Spontaneous remissions occur and treatment cannot be appraised

► [The clinical diagnosis of periarteritis nodosa is notoriously difficult and histologic examination is usually required to establish the diagnosis. Knowledge of the varied cutaneous manifestations of this disease, which, according to Lindgren and Lundmark, occur in 25% of cases, should be most helpful in the clinical diagnosis of such cases.

Treatment with cortisone and its analogues has proved very beneficial to some patients but must be continued over a long period unless there is spontaneous remission.—Eds.]

Dermatohistopathology of Various Types of Scleroderma was studied in over 200 cases by Paul A. O Leary Hamilton Montgomery and William E. Ragsdale Jr[7] (Mayo Clinic and Found.) The histopathologic changes in various types of scleroderma consist fundamentally of edema homogenization, fibrosis and sclerosis of the collagen fibers and varying sclerosis and obliterative changes in the vessels of the cutis The initial stage of edema is seen especially if the generalized forms of scleroderma are present including acrosclerosis

The collagen fibrils first reveal loss of clarity and some cloudy swelling Later there are hyalinization of the bundles and loss of distinctness of the fibrils Varying homogenization of the collagen bundles is present Granularity or fine segmenting of the bundles often occurs in all forms, but less frequently in acrosclerosis Vacuolar degeneration and atrophic changes also may occur usually at a late stage Fibrocytes are increased in a few cases of diffuse and in some localized forms of scleroderma but not in acrosclerosis. In diffuse generalized scleroderma increase in the thickness of the cutis and fibrosis of the subcutaneous tissues are greater

(7) A.M.A. Arch. Dermat. 75 78 87 January 1957

than in localized forms. In acrosclerosis there is thinning of the cutis, and atrophy of the collagen is more prominent.

The elastic tissue is characterized by an apparent increase in the number of fibers and possibly newly formed fine fibrils in almost half the cases of acrosclerosis, and less frequently in diffuse and localized scleroderma. Apparently there is a border zone between the epidermis and the elastic fibers in the cutis chiefly in acrosclerosis. Fragmentation and clumping of elastic fibers occur in varying degrees in most types of scleroderma.

Obliterative changes in the vessels are minimal in morphea and greatest in diffuse scleroderma. A perivascular infiltrate is prominent in morphea it may even be absent in other forms of scleroderma, especially in acrosclerosis.

Epidermal changes seem to be of minor importance. In acrosclerosis relative and absolute hyperkeratosis predominates whereas in morphea epidermal changes are minimal. In all forms of scleroderma an increase in melanin pigmentation occurs in the basal layer associated with an increase in melanophages in the cutis. Morphea exhibits the least increase in pigmentation.

Use of a modified McManus stain and periodic acid Schiff reaction reveals no appreciable increase in mucopolysaccharides in any form of scleroderma. Muscle specimens from patients with generalized scleroderma show obliterative changes in the interseptal vessels and secondary homogenization and atrophy of the muscle bundles with loss of cross-striation.

In the different forms of scleroderma, the pathologic differences are not significant enough to permit differentiation. The pathologic changes in any type depend on the age of the lesion and whether the disease is in the early edematous phase, the sclerotic state or in a period of involution.

▶ [These careful and extensive studies clearly show that histologic changes cannot be used for differentiation of the harmless morphea and the serious, incapacitating and often fatal forms of generalized scleroderma. Unfortunately histologic work to date has failed to provide any useful clues regarding the etiologic mechanisms in scleroderma.—Ed.]

Localized Scleroderma: Clinical Study of 235 Cases is presented by Herbert B. Christianson, Cletus S. Dorsey, Paul A. O'Leary and Robert R. Kierland (Mayo Clinic and Found.)[1] Of this group 1 patients (191) showed linear lesions or localized

[1] A.M.A. Arch. Dermat. 74:629-639, December, 1956.

curred frequently Histologic examination showed partial necrosis of the elastin sector shaped lacunae in the elastic lamina and marked inflammation of the arterial wall.

Periarteritis nodosa must be differentiated from other diseases with vasculitis In it characteristic arterial changes dominate whereas in erythema nodosum the change is in the connective tissue septa of the subcutaneous layer In erythema induratum there is subcutaneous necrosis and a pronounced tuberculoid structure.

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(7) A.M.A. Arch. Dermat. 75 78-87 January 1957

and a superficial infiltration may be palpable. In the course f involution, the white surface becomes atrophic and somewhat wrinkled.

Lichen Sclerosus et Atrophicus with Oral Involvement Histopathologic Study and Dermabrasive Treatment. Rolf F M ller (Univ of Michigan) reports a case.

W oman, 48, had many lesions of bullous lichen sclerosus et atrophicus on the back and abdomen. The genital, perianal and perineal re gions ere also invol ed. On the left buccal surface was a well-demarcated grayish white area about 2 cm. in diameter. The area was entirely smooth and soft and composed of delicate coalescent papules ithout surrounding reaction (Fig 10) A similar but smaller par tially erythematous area was present on the right buccal mucosa. Bi-



Fig 0 –Oral lesion in lichen sclerosus et atrophicus (Courtesy of Miller R. F A M Arch Dermat 43 53, July 1957)

opsy examination of skin lesions showed changes considered characteristic of lichen scleros et atrophicus. A section from the left inner cheek showed hyperkeratotic, slightly atrophic squamous mucosa with a granular cell layer The basal layer as unaltered. I places there slight acanthosis. The collagenous tissue beneath the epithelium homogenized and less densely stained and showed an increased number of blood essels. N infiltration was present. The dermabrasi technic used for the cutaneous lesions, with complete disappearance of the lesions only smooth, slightly erythematous, mind ully trophic rea emained N lesions ecurred in treated sites.

Although agreement exists as to the *clinical* and histologi ppearance of lesions of lichen sclerosus et atrophicus that ha been present for some time the observations d ffer rega ding young and early lesions. It is believed that clinically the lesion are white from the beginn ng owi g to dema beneath the *epidermis* On several occasions how er and in the p esent case early papular and macular le

¹ A M A Arch Dermat 76 43 13 July 1957

sclerodermatous plaques Group 2 patients (44) showed bilateral symmetrical disseminated plaques (generalized morphea)

In group 1 precipitating factors antecedent to onset of scleroderma included 14 instances of infection and 14 of trauma but the association was usually controversial in the latter Onset was usually slow and insidious but was rapid in several instances Arthralgias and obscure abdominal pains were common concomitant symptoms. Anomalies of the vertebral column were noted in 32 patients 20 of whom had spina bifida occulta (Anomalies of the spinal column were found mainly in group 1 patients) Many other cutaneous neurologic and congenital abnormalities were noted Complications and residua consisted of pigmentation calcinosis contractures facial hemiatrophy and unilateral atrophy of one or more extremities Duration of activity was 3½ months to 25 years The disease was benign no deaths were attributable to it.

In group 2 as in group 1 females outnumbered males 3 1 Onset was insidious and progressive. Symptoms and associated findings were similar to those in group 1 Duration was 6 months to 33 years with an average of 3-5 year Generalized morphea is not severe and prognosis is good in contrast to generalized or systemic scleroderma

► [It is interesting that the authors series includes 2 patients who also had lichen sclerosus et atrophicus which appeared several years after onset of morphea. During certain stages of development, it is extremely difficult to differentiate between morphea and lichen sclerosus et atrophicus e g plaques involving the antecubital and popliteal spaces the clavicular regions, etc., may be indistinguishable clinically At times, histologic differentiation also i difficult or impos ble —Ed.]

Lichen Sclerosus et Atrophicus of Mouth. Harold C Kays (Univ of Minnesota) and Ashton L. Welsh[9] (Univ of Cincinnati) report 3 cases One patient is believed to be the first reported with only mouth le ions whereas the other 2 patients had mouth lesions besides lesions elsewhere on the body From these case reports and personal communications with others the authors conclude that lesions of lichen sclerosus et atrophicus of the mucous membrane of the mouth are probably not so rare as wa formerly thought The primary lesion is similar to that noted on the skin viz a small white flat papule These papules may remain discrete or coalesce to form well-defined plaques are slightly raised

(9) A.M.A. Arch Dermat 76 56-58, July 1957

macular anetoderma can be assumed. In certain types of morphea (morphea alba plana) marked atrophy exists rem nant of the lilac ring or pigmentary halo as well as th absence of ballooning lesions or lesions with herniation permit the differentiation of this type of morphea from mac ular anetoderma. Occurrence of macular anetoderma after lichen planus must be distinguished from lichen sclerosus atrophicus Macula anetodermas also occurring in various other dermatoses e.g erythema multiforme sarcoid (Boeck) psoriasis, parapsoriasis, trichophytosis, etc. are probably coincidental In certain cases of urticaria telangi ectasia and purpura, however transition into subsequent macular anetodermas are assumed (Touraine)

Hist logy hardly permits distinction between different types of macular anetoderma. The inflammatory phase re- eal marked edema in the Schweninger Buzzi and P lli zari types. In this phase polymorphonuclear infiltrates are seen, part cularly in the Jadassohn and Pellizzari forms and ther re some minor lymphocyt accumulations in the atrophic phase of all types. In macular anetoderma associated with yphil s, nfiltrates contain numerous plasmocytes Capillarite atroph cante with or without telangiectasis he s ign ficant capillaritis particularly n the inflamma tory phase The terminal phase reveals a circumscribed disappearance or ra faction of elastic tis ue n all types.

Pseudoxanthoma Elasticum (Grönblad-Strandberg Syndrome) Clinical, Light and Electron Microscopic Study P Ronald Loria C Barrett Kennedy James A Freeman d \ Medd Hen ngton[a] (Charity Hosp New O leans) re ort case

W man, 49 had skin changes on the neck, axillae and perineum since age 13 The skin in the involved areas lay in folds along the nor mal lines of the skin (Fig 11) Hair growth in the axillae and peri neum somewhat decreased I the skin of the neck were many superficial pinhead to pea sized, firm, cream-colored nodules that presented an appearance Ophthalmoscopic examination revealed angioid streak bilaterally The blood pressure was 180/94 mm Hg Radial pulsation er decreased, and no ulnar artery pulsations could be obtained Femoral artery pulsations were decreased, popliteal nd dorsali pedi pulsations ere barely perceptible and no posterior tibial artery pulsation could be felt.

Several months later she was hospitalized because of hematemesis. Gastroscopic examination revealed superficial incompletely healed ulcer with ssociated gastritis. Subtotal gastrectomy was done. No

[a] M A Arch Dermat 76 609-618, November 1957

sions have been noted to be erythematous or brownish apparently because of presence of an infiltrate beneath the epidermis composed of lymphocytes, histiocytes and fibroblasts On correlation of the clinical and microscopic features observed in early lesions it seems that presence of an infiltrate is a characteristic primary feature of the disease and that the edematous zone of homogenization develops thereafter

► [It is fortuitous that 4 cases of a condition so rarely reported as lichen sclerosus et atrophicus of the oral mucous membranes should be reported in two articles, one following the other in the same dermatologic journal —Eds]

Macular Anetodermas After a thorough study of about 200 observations published during 1884-1953 R. DeLuzenne[2] (Paris) proposes the following new classification (1) Primary macular anetodermas appear on a previously normal skin and include (*a*) isolated or cryptogenetic types, comprising benign pseudotumors (Schweninger Buzzi) erythematous anetoderma (J Jadassohn) erythema urticans and atrophicans (Pellizzari) (*b*) types associated by coincidence direct or indirect relation with certain general diseases or infections such as syphilis and tuberculosis, or endocrine disturbances and certain dermatoses, such as acrodermatitis atrophicans (Pick Herxheimer) and possibly lupus erythematosus (2) Secondary macular anetoderma follow in loco dermatoses which include syphilids, tuberculids urticarial lesions and purpuric or telangiectatic manifestations (capillarite atrophicante Touraine)

Pseudotumors (Schweninger Buzzi) are characterized by the absence of inflammatory phenomena in the initial stage whereas initial lesions of other forms of primary macular anetodermas show erythematous macules or papules with or without pruritus The zones of extension also show erythematous borders In the atrophic stage balloon like lesions and herniation are characteristic In associated types in which *macular anetodermas may follow* a secondary syphilitic eruption or occur in patients with tuberculosis, toxic or neuroendocrine effects are assumed. The association of macular anetoderma with lupus erythematosus puerperal infections, hypertrophic endometritis and cirrhosis are probably coincidental or at least hypothetical. Because of clinical histologic and etiologic reasons a relation between acrodermatitis atrophicans (Pick Herxheimer) and

(2) Ann. dermat. et syph 83 618 630 Nov Dec 1956.

cification of the major blood vessels and extensive calcinosis of the subcutaneous tissues. This appears to be the first case reported with extensive calcinosis of the subcutis in association with pseudoxanthoma elasticum. Calcification is common in the basophilic degenerated fibers of the skin and is a prominent feature of the arterial involvement in systemic elastic disease, so it does not seem too strange to find calcification in the subcutaneous tissues as a feature of this process.

The second case is one of Paget's disease associated with

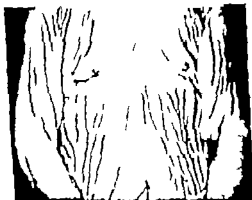


Fig 11 Pseudoxanthoma elasticum with arterial involvement and calcinosis of panniculus. Pronounced looseness of skin had resulted in pendulous folds. (Courtesy of Shaffer B et al A.M.A. Arch Dermat. 76:622-633, November, 1957)

angioid streaks of the retina and pseudoxanthoma elasticum. Although Paget's disease has often been described in connection with angioid streaks, only 1 case has been reported with the triad of Paget's disease, angioid streaks and pseudoxanthoma elasticum. Inasmuch as angioid streaks are well established as a manifestation of systemic elastic disease, the authors feel that the triad is a valid entity. Perhaps this association has not been noted heretofore because of the rarity of pseudoxanthoma elasticum and the failure of many students of Paget's disease to note this cutaneous lesion.

It is now recognized that pseudoxanthoma elasticum is the cutaneous expression of a generalized disturbance (probably genetic) of what appears with ordinary staining to be the elastica. Some authors recently challenged this opinion and feel that the fibrous elements affected are collagen fibers.

vessel changes were noted in the stomach specimen, and elastic tissue stains revealed no change in the connective tissue. Typical elastic tissue degeneration was found in a specimen of obviously involved skin from the neck, and typical changes in the middle and lower corium compatible with pseudoxanthoma elasticum were noted in grossly normal appearing skin on the lateral aspect of the right arm. Electron microscopic studies of tissue from the neck showed normal collagen tissue and degeneration of the elastic tissue with calcium deposition. Histologic examination of a cream-colored nodule from the neck revealed a calcifying sebaceous cyst.

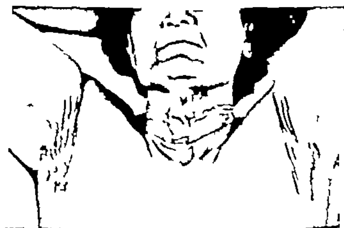


Fig. 11. (Courtesy of Loria, P. R., *et al.* A.M.A. Arch. Dermat. 76:609-613, November 1957.)

The systemic nature of pseudoxanthoma elasticum has been repeatedly shown. In this case systemic vascular involvement is suggested by decreased or absent peripheral pulsations and presence of hypertension. Gastrointestinal bleeding further shows this involvement.

Pseudoxanthoma Elasticum: Cutaneous Manifestation of Systemic Disease. Report of Case of Paget's Disease and Case of Calcinosis with Arteriosclerosis as Manifestations of This Syndrome is presented by Bertram Shaffer, Herbert W. Copelan and Herman Beerman[4] (Univ. of Pennsylvania). In one patient the cutaneous manifestations were widely generalized (Fig. 12) involving all the skin except the scalp, palms and soles. Pronounced looseness of the skin was present, with accentuated cross hatchings and markedly deepened furrows. There was extensive peripheral vascular disease, gangrene of the lower extremities, widespread cal-

(4) A.M.A. Arch. Dermat. 76:622-633, November 1957.

process is likely a deficiency of thyroid hormone (or its tissue-active form) at the periphery

► [The results of this study appear contrary to accepted theories concerning the pathogenesis of localized myxedema. Based on these findings, the use of triodothyronine (Cytomel®) should be particularly beneficial in the treatment of this disease.—Eds.]

Specificity of Kveim Reaction. Recently data were published purporting to show that the Kveim reaction is essentially without diagnostic specificity Carl T Nelson and Benjamin Schwimmer[4] (Columbia Univ) summarize results with the Kveim test in 335 persons during the past 7 years, using a single lot of Kveim suspension of established reactivity and specificity The antigen was prepared from microscopically proved sarcoid spleen tissue. Some suspension prepared from histologically typical sarcoid tissue may be totally inert when tested Others are nonspecific, and still others are satisfactory for a time only to lose their specificity or capacity to produce reactions

The Kveim reaction was positive in 53 (74%) of 72 patients with biopsy-confirmed sarcoidosis Of 56 tested during the active phase of the illness all but 3 gave positive results. Of 29 with typical clinical x ray and laboratory findings of sarcoidosis in whom no cutaneous lesions or enlarged lymph nodes were available for biopsy the reactions were positive 17 (59%) In this group 3 of 20 patients with clinically active disease failed to react to the antigen. Only 1 of 35 in a probably not sarcoid group reacted positively These patients exhibited various clinical findings, 1 or more of which are sometimes associated with sarcoidosis. The Kveim reaction was positive in 1 of 99 with active tuberculosis. Of 82 patients with other diseases and 18 normal persons none reacted positively In all therefore, false positive reactions were observed in only 2 of 234 persons without sarcoidosis

These studies indicate that the Kveim reaction is highly specific for sarcoidosis and that it is infrequently positive in other diseases. It tends to become negative as sarcoidosis enters a stage of remission. Sometimes patients who are judged clinically to be in remission continue to have a positive reaction, whereas a few with obvious progressive disease fail to react to the intracutaneous test.

► [An excellent study which should go a long way to clear up some of the mysteries about the Kveim test. This test has a high degree of specificity but is negative in a substantial minority of cases with proved sarcoid

(4) J Invest. Dermat. 30:11, January 1958

The tissues predominantly involved are the midcutis (sometimes the mucosae also) the media and, to a lesser extent, the intima of the blood vessels and Bruch s membrane of the eye This results in (1) pseudoxanthoma elasticum, (?) calcinosis dilatation aneurysm and rupture of the blood vessels and (3) angioid streaks and choroiditis.

Histogenesis of Myxedema. J L. Gabrilove and A. W Ludwig[5] (Mount Sinai Hosp New York) did histochemical studies of the skin changes in 6 patients with primary thyroidal myxedema, 6 with myxedema secondary to hypopituitarism and 7 controls without thyroid or other endocrine disease Punch biopsy specimens were obtained, usually at weekly intervals.

The findings were similar in the primary and secondary myxedema and consisted of the extracellular deposit of metachromatically stained material interpreted as a mucopolysaccharide-protein complex. The amount of material present in the tissues was dependent on the degree and duration of the thyroid deficiency In previously untreated patients with large deposits of metachromatic material, treatment with desiccated thyroid resulted in a significant diminution of the deposit within 2 weeks but 6-8 weeks was required for complete elimination of the excessive mucinous matter If inadequate dosages of desiccated thyroid were used residual material remained visible indefinitely After omission of therapy in patients with marked thyroid deficiency 3-5 weeks elapsed before changes in the skin again became apparent histologically This interval was not long enough to permit the appearance of clinically evident myxedema.

Since all previous investigations of the histologic changes in the myxedematous process were based on studies of tissues from patients with primary or localized myxedema, it is probable that the deposit of mucoprotein is the result of the action of elevated levels of thyrotropin or an associated pituitary fraction directly on the connective tissues with a consequent increase in the local production of mucopolysaccharides This concept is no longer tenable in view of the finding in this investigation of identical changes in the skin of patients with pituitary deficiency in whom circulating levels of thyrotropin must be extremely low or absent. Therefore the factor which initiates the myxedematou

(5) J Clin. Endocrinol. 17:925 932, August, 1957

tensely painful nodules appeared simultaneously on both legs and the right arm. On two or three occasions, some of them had become ulcerated and had left cicatricial lesions in the form of pigmented macules. Various methods of treatment have been tried at different times without success, although some produced transient improvement.

Opinions differ as to the specific cause of the syndrome, but in general it seems to be the result of a systemic allergic reaction. Tests for allergy in the author's patient produced the following results: tuberculin, intensely positive; various bacterial extracts, 4+ and *Candida albicans*, 2+. An attempt is now being made to desensitize the patient to these organisms.

► [It would be interesting indeed if the agents producing the positive skin tests had any bearing on the etiology of this disease. Without corroborating evidence there is no *justification for this assumption*.—Eds.]

Granulomatosis Disciformis Chronica et Progressiva (Miescher).—Histologic entity has been confirmed in several publications though classification of this condition remains obscure. Clinically it resembles sclerodermiform hypodermatitis or lipoidal necrobiosis. A case reported by Fr. Woringer and A. Ullmo[4] (Strasbourg) is an absolute replica of those cases which have been observed by other investigators.



Fig. 11.—Clinical appearance of chronic, progressive disciform granulomatosis resembling sclerodermiform hypodermatitis or lipoidal necrobiosis. (Courtesy of Woringer, F., and Ullmo, A.: Ann. dermat. et syph. 8: 22-28, Jan.-Feb., 1937.)

(4) Ann. dermat. et syph. 8: 22-28, Jan.-Feb., 1937.

disease. Several of the Kveim antigens tested by Nelson and Schumann either proved to be inert or lost their specificity or potency after many months.]—Eds.]

Weber Christian Panniculitis with Areas of Sarcoidal Structure According to Jose Kriner[7] (Hosp. Israelita, Buenos Aires) Weber-Christian panniculitis is either uncommon or seldom diagnosed. Clinically it is characterized by hypodermic or dermohypodermic nodules varying in size number appearance and localization In most cases, the overlying skin is erythematous and the nodules are palpable and painful on pressure They are generally adherent to the deeper structures and their consistency is firm and elastic. They rarely become ulcerated. The smallest ones usually disappear without a trace, but large nodules leave a characteristic depression by which a diagnosis can be made in retrospect The syndrome is usually marked by fever with irregularly recurring attacks characterized by chills, general malaise joint pains nausea vomiting headache and myalgia Splenomegaly and leukocytosis are sometimes noted

A positive diagnosis can usually be made quite easily but in recent cases in patients with few symptoms or in absence of histopathologic study it may be necessary to differentiate between this condition and erythema nodosum erythema induratum periarteritis nodosa nodular syphilid, hypodermic leproma, hypodermic sarcoid of the Darier Roussy type nodular toxicodermas (caused by halogens or sulfonamides) cutaneous streptococcic conditions and foreign body granulomas. The histologic picture varies according to the stage of the disease, because the underlying process is one that is essentially dynamic and progressive The three stages in its development are the acute inflammatory the macrophagic and the fibroblastic. The first of these is the stage of clinically apparent induration the last in which there is a tendency toward fibrous cicatrization may appear in some lesions while other lesions in the same patient are in a different stage of development

An additional finding revealed by biopsy of an active nodule in a woman aged 47 consisted of areas of sarcoidal structure in the hypoderm The illness had begun several years earlier with subjective symptoms of itching and burning in both legs. A few months later various sized and in

(7) Arch. argent. dermat. 7 125 135 June 1937

100 cc. Serum cholesterol and phospholipid levels were normal or somewhat above the upper limit of normal. Plasma protein levels were normal. Extensive histologic and histochemical studies revealed the essential lesions to be degeneration and destruction of elastic fibers and appearance of argyrophil fibrils throughout the dermis, hyalinosis of the upper layers of the dermis beginning around small arterioles of the sweat glands, and nodular hyalinosis of the oral mucosa. The hyalin apparently contained carbohydrate but little or no



Fig. [illegible] Nodular and scarring lesions of face. Note absence of eyelashes and scarring lesions [illegible] courtesy of [illegible] and Archives of Dermatology [illegible] A. M. A. Arch. Path. January 19[illegible]

protein. Acidic rest[illegible] were probably present in the early period of hyalin formation. [illegible] of full developed hyalin, no evidence of acidic rest[illegible] was obtained, indicating that their presence was a transient stage in hyalin formation.

In contrast to the earlier report of the case by Urbach, no lipids could be identified within the moderate quantity of sudanophil material demonstrable. The fat deposit appeared to be composed of neutral fat.

Since Urbach's review in 1932 on the then known cases the presence of lipid within the tissue lesions has been considered by most author[illegible] to be an expression of a disturbance

Man, 32, without history of trauma, noted a lesion on the anterior surface of right leg. At first, it was a small reddish plaque, but by 10 months it had increased to 6.5x4 cm. and displayed a polycyclic contour. The center was chamois yellow with a purplish border 2-3 mm. wide. Hairs were lacking on the lesion, which was also strewn with whitish scales (Fig. 13). On palpation, a sclerodermiform infiltration contrasted with pliability of the surrounding skin. Serologic test [illegible]

Microscopic appearance of chronic, progressive disciform granulomatosis is sufficiently characteristic to prevent confusion with tuberculosis or the Besnier Boeck Schaumann syndrome. Absence of fibrinoid necrobiotic plaques eliminates granuloma annulare and lipoidal necrobiosis.

Various treatments have been tried without definitive results. The authors suggest that the lesion may be due to a metabolic disturbance. It appears that liberation of some endogenous substance and its presence in the tissues may give rise to a "foreign body granuloma."

► [Even though quite a few cases of this dermatosis have been described since Miescher and Leder's original description in 1948, no progress has been made in elucidating its etiology. Miescher and Leder felt that, histologically, the lesion resembled tuberculosis, tertiary syphilis and Boeck sarcoid. They considered it to be atypical tuberculosis."—Eds.]

Hyalinosis of Skin and Mucous Membranes (Urbach-Wiethe's Lipoidproteinosis): Histochemical Study of Case 28 Years after Its First Publication is reported by H. Ungar and I. Katzenellenbogen[9] (Hebrew Univ., Jerusalem).

Woman, 56, had pruritus vulvae. She had had first skin lesions at age 10. At age 28, while she was under the observation of E. Urbach, a diagnosis of lipoidosis cutis et mucosae was made. Over the years, the lesions had become more widespread, and recently shallow ulcers had appeared in several areas of the skin and oral and vaginal mucosae.

On examination, yellowish nodules, 1-3 mm. in diameter, covered the skin of many areas, including the entire face, particularly around the eyes (Fig. 14), neck, trunk, armpit and several fingers. Below the elbows and over the tibial tuberosities, confluent hyperkeratosis was present besides the yellowish nodules. The skin of the face, neck and back was pitted, wrinkled and covered with innumerable small scars. Hair was absent over all areas containing nodular or scarred lesions. The oral mucosa was studded with yellowish papules and small elevated plaques of firm consistency. Laryngoscopy revealed similar lesions on the vocal cords.

Mild glycosuria was present, and fasting blood sugar was 178 mg./

(9) A.M.A. Arch. Path. 63:65-74, January, 1957.

teinemia may be present at times, but their significance is not known. Congenital irritability or fragility of the termi nal vessels may account for the transudation of lipids and/or proteins into the surrounding tissues, finally de troying and replacing the elastic and collagenous fibers. There s no effective treatment although improvement has been reported after administration of lipocaic.

Woman, 57 had always been hoa se. At age 14 several small yellow lesions ppeared on the eyelids. At age 51 papular lesions developed in the axillae. Four years later laryngoscopic examination re ealed thickened vocal cords and a cauliflower-like enlargement of the tip of the epiglottis. At this time she had convulsive seizures and psychomotor disturbances. The skin appeared yellowish white and waxy. The hair was thin and dry and the eyebrows sparse. There were many translucent papules on the eyelids and similar larger lesions on the inner surfaces f the lips, buccal mucosa, soft palate and posterior portion of the pharynx and tongue. Laboratory findings were essentially normal except for basal metabolic rate of —11% and a sedimentation rate of 33 mm./hour Many lesions from arious areas ere examined histologically all corresponded to the description noted earlier T sues from the tongue and axilla were negative for amyloid The hyaline material w shown to be a polysaccharide by means of amylase digestion followed by the Hotchkiss-McManus stain.

▸ [As is stressed once mor here by Laymon and Hill, hyalinosis cutis et mucosae, also called lipoidproteinosis, may be accompanied by visceral involvement If the convulsiv seizures and psychomotor disturbances in their patient were due to involvement of the brain, then this represents to our knowledge the first such instance reported —Eds.]

Lipoidproteinosis-Porphyria Connections between the Two Processes. Julio M Borda, Jorge Abulafia and Alberto I Cars lbo[3] (Buenos Aires) report on 3 men, aged 58 42 and 60. Typically porphyric symptoms found in the authors patient and cases reported i the literature includ scars and bullae that later give way to scars It s of interest that th ma festations of lipoidproteinosis may exacerbate dur g the ummer and that in patient w th lipoidproteinosis of diff se pigmentati ns r elastoidosis sclerodermiform pla ques erosion and hypertrichosis of the eyelashes all of wh ch re frequently found i the porphyrias, occur

\ urvey of cases warrant the statement that lipoidprot nos d porphyria are often associated, though th exist en f uch a association ha hitherto been unsuspected, a d plains some f th unu ual haracteristics of l poidpr teinos The l nical fact in the authors cases indicate

(3) Arch argent dermat. 4 229-251, September 1954.

of lipid metabolism Urbach when studying the present case and others characterized the deposits as phospholipids, but it appears that during the time that has elapsed, the fat deposits have changed not only in amount but also in quality and are now composed probably of neutral fats. This conclusion is supported by the negative results of Baker's acid-hematein method for phospholipids the Schultz reaction for cholesterol and absence of anisotropic crystals in unstained frozen sections Absence of lipids was further confirmed by results of the periodic acid Schiff procedure

Neutral fat was found in plaques of degenerated elastica and along the course of hyalinized fibers in poorly vascularized areas of the dermis suggesting the origin to be in degenerated fibers of collagen and elastic tissue which normally contain bound fatty substances Similarly it appears likely that the hyaline changes are the result of faulty metabolism of collagen and elastic fibers leading to the unmasking of carbohydrates

► [This follow up study of one of Erich Urbach's original cases by means of newer histochemical methods is most interesting —Eds.]

Appraisal of Hyalinosis Cutis et Mucosae is presented by Carl W Laymon and Elmer M Hill[1] (Minneapolis) The characteristic cutaneous lesions are polymorphous, yellowish white papules usually present on the face neck hands and eyelids giving a beaded appearance pustular or bullous lesions followed by crusts on the face and upper extremities and verrucous plaques and atrophic scars on the face elbows and knees Mucosal lesions uniformly present are yellowish infiltrations of the tongue lips buccal cavity pharynx and larynx, which may produce dysphagia, hoarseness or difficulty in protruding the tongue Other less common findings are alopecia dental abnormalities and visceral involvement

The disease is regarded as a genodermatosis familial and related to consanguinity Histologically there are no constant epidermal changes but the corium is permeated by homogeneous material particularly around blood vessel and appendages The process of hyalinization destroys both the elastic and collagenous fibers in the areas affected Laboratory findings have not been constant as to lipid or protein disturbances although several patients have shown a tendency toward latent diabetes Dyslipoidemia and dyspro-

(1) A M A Arch Dermat 75 55-65 January 1957

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(2) Arch argent dermat. 239-291, September 1 16.

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Among other things the connections between lipoidproteinosis and porphyric changes revealed by the study provide an explanation of the tendency toward diabetes or its actual presence in many patients with lipoidproteinosis or porphyria The concurrent manifestations were observed not only clinically but also by histopathologic and histochemical studies which established the closeness of the connections between the two conditions that were formerly regarded as completely independent. In both the epidermal changes appear to be secondary to and consequent to changes in the underlying dermal connective tissue Discrete atrophy or even hyperacanthosis with hyperkeratosis can be seen in both As lipid infiltration demonstrated for the first time in patients with porphyria by the authors is not always present in all parts of the skin repeated studies must be made in patients in whom the two conditions are associated before lipoidproteinosis can be excluded from the diagnosis

Two Cases of Cutaneous Amyloidosis are reported by Alejandro A Cordero Julio M Borda and Sergio G Stringa[1] (Buenos Aires) Primary amyloidosis is independent of any earlier chronic condition In localized forms the amyloid substance is deposited exclusively in the skin or in the viscera (bladder urethra pharynx, tongue, eyes lung) In generalized or systemic forms visceral deposits are found predominantly in the mesenchyma of the cardiovascular system gastrointestinal tract muscles tongue joints and lymphatic system When the skin is affected the lesions, which are usually found on the face (periorbital region) assume a sclerodermic or xanthomatous aspect Papules nodules petechiae and ecchymoses may appear Prognosis is poor

Secondary amyloidosis is always associated with some chronic condition (tuberculosis bronchopulmonary suppuration osteomyelitis leprosy syphilis etc.) of which it is a result In generalized forms of secondary amyloidosis the skin is usually not affected The visceral lesions appear in the spleen liver kidney and adrenals Prognosis is poor

(1) Arch. argent. dermat. 6 293-305 September 1956.

All clinical forms of amyloidosis—primary or secondary—may affect the skin, but in most cases of cutaneous amyloidosis the condition is primary Apart from the lesions of the systemic form already referred to the skin lesions appear electively on the legs and may be classified as (1) lichen amyloidosus (2) amyloidosis moniliforme and in plaques and (3) hypertrophic corneous amyloid lichenification, which is not a true clinical type but the result of lichenification of the other two types of lesions caused by excessive tching and scratching which gives it a different appear a ce Occasionally a rare fourth type can be seen the mac ular form described by Palitz and Peck in 1952

Diagnosis of amyloidosis especially of the cutaneous variety is based on history and general examination. The Benhold test and its variant the Nomland test and, most of all histopathologic findings. The authors patients 2 men aged 70 and 27 had primary cutaneous amyloidosis of the second type e moniliforme and in plaques localized on the chest, back and shoulders. Diagnosis was established by the Nomland test in 1 and by histopathologic findings in both. Treatment with dehydrocholic acid, prednisone bromides, podophyll n and other preparations was ineffectual and the dermatosis remai ed unchanged in both patients.

Colloid Milium was studied by the application of paper hromatography (Zoon t al 1955) by J F Becker and Harold T H Wilson (Middlesex Hosp London) They report 3 cases in which the small translucent yellowish papular lesions were noted on the backs of the hands, the forehead nd cheeks and the bridge of the nose and cheeks, respect ly H stologically all biopsy specimens showed the haracteristics of colloid m'li m, masses of pink-sta n ng colloid lying between the follicles in the upper dermis

Colloid material taken from lesions of the 3 patients was compared with collagen, elastin and serum proteins from lotted blood. The results confirm the previous observation that the mino acid composition of the colloid bears a closer imilarity t serum proteins than it does to either collagen or lastin. Notably hydroxyprol ne was found to be absent from colloid and serum proteins but was present in both collagen a d lastin. In addition, cyst n and methionine were found in the colloid and serum proteins but not in col

( ) Brit. J. Dermat. 68 345-349 November 1956.

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(4) Brit. J. Dermat. 68:345-349, November 1956.

lagen or elastin It is concluded that there is substantial evidence, but not positive proof in favor of the theory that colloid is derived from serum proteins.

Psoriasis and Heredity was studied by K. Hoede[3] (Wurzburg Germany) The high incidence in the teens and closely following years (table) might imply environmental and occupational influences in the etiology of psoriasis. However this is only an assumption while other facts speak clearly for a hereditary origin The opinion of most authors that psoriasis is a familial hereditary disease can be proved by

Onset of Psoriasis in 2,717 Patients

Age	Total		Men		Women	
	No.	%	No.	%	No.	%
0-9	396	14 6	167	12.0	229	17 9
10-19	987	36 5	413	29 4	574	44 5
20-29	728	26.8	464	33 1	264	20 5
30-39	310	11 4	211	15 0	99	7.8
40-49	168	6.2	106	7.5	62	4.8
50-59	84	3 1	48	3.4	36	2.8
60-69	36	1.2	18	1.3	18	1.5
70-79 (including 1 of age 83)	8	0.2	5	0.3	3	0.2
Total	2,717		1 432		1,285	

the family history in at least 50% of the patients. Among 20 patients with psoriasis followed for 30-60 years the disease was hereditary in 16

The heredity of psoriasis may be on a dominant or recessive basis. If both parents have psoriasis the chances of the children getting the disease are 1 4 to 1 3 With an increasing number of children the number of psoriatic children in the same family decreases Studies on homozygotic twins with psoriasis point also to the hereditary nature of the disease

In general there are no known endogenous or exogenous factors which would precipitate the development of psoriasis. The only known factors which may affect the course of the disease are the sex glands especially in women This is well seen by the influence of menarche pregnancy and menopause on psoriasis

The ineffectiveness of all known forms of treatment in changing the natural course of psoriasis as well as the un

(3) Hautarzt 8 433-438, October 1957

predictable recurrences and relapses also indicates a hereditary disease The number of permanent cures about equals the number of spontaneous, lasting remissions.

The fact that psoriasis is rare in married couples speaks against a possible infectious etiology Among 3,719 patients with psoriasis, observed over 75 years, there were only 6 instances in which husband and wife were both suffering from psoriasis.

► [The high incidence of onset of psoriasis in patients under 10 years of age will undoubtedly come as a surprise to others, just as it did to us. Even the high incidence between the ages of 10 and 19 is somewhat surprising. To our knowledge, this report constitutes the largest number of cases of psoriasis accumulated for such a study We wonder however if the age incidence of psoriasis is the same in the United States, we are of the impression that there are fewer cases in the first two decades and more between ages 30 and 50.—Eds.]

Roentgen Manifestations of Psoriatic Arthritis. Thomas F Meaney and Robert A Hays[4] (Cleveland Clinic) group the roentgen findings in 15 patients having psoriasis and arthritis into two categories. In the first group composed



[illegible] 13.—Articular erosion in terminal interphalangeal joint of fourth finger and, to lesser extent, third finger. There is [illegible] erosion in proximal interphalangeal joint of fourth finger. ([illegible] of Meaney, T. F., and Hays, R. A.: Radiology 68:403-407, March, 1957.)

[4] Radiology 68:403-407, March, 1957

of 11 patients, the usual roentgen manifestations of rheumatoid arthritis were apparent. These consisted of generalized demineralization of bone narrowing of the joint spaces, some erosion about the articular surfaces and soft tissue swelling about the involved joints. These changes predominated in the proximal interphalangeal joints. The findings in this group are designated psoriasis with rheumatoid arthritis

In the second group were 4 patients with changes atypical for rheumatoid arthritis The x rays revealed (1) lack of generalized demineralization of bone, (2) destructive changes in the terminal interphalangeal joints (Fig 15) without associated involvement of the proximal joints or with minimal involvement and (3) destructive changes in the terminal interphalangeal joints associated with hypertrophic changes about these joints but differentiated from osteoarthritis by the presence of severe articular destruction. The findings in this group are designated psoriatic arthritis The authors believe that changes found in the x rays in this group represent a distinct type of arthritis

► [It seems to us that most experts are of the opinion that psoriatic arthritis is a distinct entity (see also Sherman, M S J Bone & Joint Surg 34-A 831 1952) —Eds.]

Psoriasis and Arthritis in relation to each other were studied by V Wright[7] (Stoke Mandeville Hosp) The Waaler Rose Differential Agglutination Test (D.A T) has been used to distinguish uncomplicated rheumatoid arthritis from erosive arthritis with psoriasis. (The term erosive arthritis" replaces rheumatoid arthritis to avoid prejudging the lesion) Erosive arthritis occurs in about 6% of psoriatic patients roughly twice as often as in the general population. In this series it occurred in 18 men and 16 women The sites of predilection of the cutaneous manifestations were the same in patients with or without arthritis as was the percentage of occurrence of nail changes In only 1 patient with psoriasis and arthritis were subcutaneous nodules found, a lesion considered to be characteristic of rheumatoid arthritis

A modified technic of Rose and Heller was used for the D.A T in this series. The result was positive in not less than 80% of patients with rheumatoid arthritis and only in a small percentage of those with nonrheumatoid arthropathies Of the patients with psoriasis and erosive arthritis

(7) Brit. J Dermat 69 1 10 January 1957

only 2 gave positive reactions i.e. 94% were negati e. It is uggested that in those with a negative result the arthritis either is modified by the psoriasis or more probably is a distinct entity

Th major features of erosi e arthritis associated with psoriasis compared with uncomplicated rheumatoid arthriti are (1) t tended to be milder than rheumatoid arthritis (2) the joint distribution was similar but a predilection for the distal nterphalangeals occurred with nail changes and (3) there was a high incidence of sacroiliac joint in olve ment.

There were several significant cutaneous manifestations in the arthritic group the psoriasis was u ually not extensi e although f so the arthritis was severe palms and soles were generally not affected n no patient was pustular psorias present and the psoria i was not res tant to treatment ex cept n patients with sev re rthritis.

► [One could add that psoriasis of unusual forms, g with pustules, are more apt to occur in patients ith associated arthritis. W hav found as many cases of psoriasis that ere difficult to treat or treatment resist ent among psoriatic patients without arthritis as among those with arthritis. —Eds]

Psoriasis of Hard Palate Report of Case ; presented by Arthur Norris (Chicago) and Howard Yaffee[8] (Ann Ar bor Mich.)

Man, 61 had widespread psoriasis All the nails wer in olved, and there was bulbous enlargement of the terminal phalanges of all digits but no discomfort in the lesions or pains in the joints. In the buccal cavity there was a mottled dusky erythema involving both hard and soft palate A biopsy section of an involved area showed parakeratosis, thinning of the suprapapillary epidermal plates and elongated rete ridges with clubbing all compatible with psoriasi The skin responded rapidly to treatment w th the Goeckerman regi men, and there was concomitant fading of the erythematous lesions of the palate.

The patient gave history of extensive psoriasis associated with hoarseness 7 years previously At that time glossiti and dusky erythema of the oral, pharyngeal and laryngeal mucosae were present. Hoarseness and skin lesions cleared with local measures and chemotherapy but palatal erythema persisted. On 3 other occasions during the next 7 years the patient was hospitalized for treatment of extensive psoriasis, and trophy of the papillae of the tongue and palatal erythema were noted

In the few reports of psoriasis of the oral mucous membranes in the literature, the lesions have been variously de scribed as being white to yellow plaques. They assum the

(8) A.M.A. Arch. Dermat. 74 337 338, September 1957

more characteristic picture of psoriasis on the lips where drying has occurred In most of the reports the mucous membrane lesions were accompanied by typical cutaneous lesions, and in several cases clearing of the oral lesions paralleled clearing of the cutaneous lesions

► [Another lesion which should be kept in mind in the differential diagnosis of eruptions of the oral mucosa. Since the oral mucosa is usually not inspected in routine examinations for psoriasis, it appears possible that the incidence of psoriasis of the mouth is higher than we know —Ed.]

Koebner's Phenomenon in Study Concerning Primary Epidermal Pathogenesis of Psoriasis. Numerous studies of the dehydrogenase (DH) activity in tissue have revealed that the degree of activity is proportional to the vitality of cellular metabolism. Where there is maximum cellular activity and rapid regeneration as in the hair follicle and the sweat and sebaceous glands the DH reaction is always strongly positive. Adolf Kuta and Emil Neumann[9] (Charles Univ Prague) studied the DH activity in skin that had been irritated by scratching with a hypodermic needle Six to nine days after scratching pieces of skin were excised for histochemical study At this time before psoriatic papules had formed in response to the external trauma skin from patients with psoriasis showed increased DH activity in the epidermis At the margins of the scratched area where no irritation occurred the DH reaction was negative. It was also negative in skin from the buttocks and wrist of patients without psoriasis The DH reaction was positive in 2 of 4 biopsies from the skin of the knee of normal controls and was strongly positive in psoriatic papules It has been shown by others that skin from the knee has an unusually high capacity of regeneration.

The authors believe that the finding of increased DH activity in irritated epidermis of patients with psoriasis together with negative results in skin from psoriatics that has not been irritated and in normal skin gives evidence of a primary epidermal pathogenesis of the psoriatic process. The psoriatic process appears to be a disorder resulting in accelerated regeneration of the epidermis The process tends to occur more frequently in areas such as the elbows and knees which are known to have a high capacity of regeneration. The accelerated exchange of the epidermal layers coinciding with an intense metabolic activity of the epidermal cells

(9) Dermatologica 115 51-60, July 1957

explains the occurrence of parakeratosis. In the light of this pathogeneses the favorable results obtained w th therapeu tic measures which can directly affect the karyokinetic ac tivity (tar arsenic, x-rays, ultraviolet rays) or suppress by their reductive influence the oxybiotic processes necessary for proliferation (tar mercury) are easy to explain.

► [Utilization of the Koebner phenomenon (isomorphic response) to study the pathogenesis of psoriasis, lichen planus, etc., seems sensible. —Eds.]

Intractable Pustular Eruptions of Hands and Feet Review of 70 Patients to assess the role of focal sepsis was done by Joh Everall[1] (Gen'l Infirm Leeds) Intractable pustu lar eruptions of the hands and feet present as several patterns called pustular bacterid, pustular psorias s and an abortive form f acrodermatitis perstans. The essential features of the pu tular bacterid type are discrete pinhead sized lakes of pus which dry t brown macules with scaling and erythema the affected skin often developing a red glazed appearance. I itially th lesions usually invol e the center of the palms d soles, but they may pread to include the entire flexor aspect of the hands and feet.

Pustular psorias s (Barber) consists of scaling psoriasi form areas in which pinhead-sized intraepidermal pustules form a d later develop into yellow spongy cru ts which on emov l disclose a red glazed skin with innumerable lakes of pus Sites f election are the em nences of the hand and ner part of the soles often spreading to the center of the palm a d soles. Outlying patches may occur on the digits, including the kin around the nails.

In the bortive form of acrodermatitis persta s there are small solitary well-circumscribed areas of pinhead-sized lakes of pus which dry to brown macules with very little su rounding inflammatory reaction. They occur on the thenar eminences and the inner part f the soles and ar usually confined t the same reas for years.

These three types of eruption are probably of the same fun damental significa ce and represent an individual pattern f reaction, p obably combination of psoriasis with an or dinary catarrhal eczematization. Microscopi d cult ral xamination of the pustules for micro-organ sm i invaria bl negative

Of 70 pat ents with intractabl pustula eruptions of the

(1) Brit. J. Dermat. 69:269-272, July-Aug. 1957

hands and feet 23 (33%) were found to have a septic focus. The focus was removed in 18 patients, with clearing of the eruption within 6 months in 2 cases. In 6 others there was temporary clearing followed by relapse. Of the 5 patients in whom the focal infection was not removed, 3 cleared and remained clear for 6 years or longer. In the other 2 the eruption has remained active for 1 year or more.

In 4 of 47 patients with no focal sepsis the eruption cleared after lasting 1-6 years and has remained clear for 6 months to 5 years. Of the other 43 12 improved. The relative proportion of patients cured and of patients who still had active disease is the same in the group with and the group without focal infection. This suggests that removal of foci of infection played little or no part in producing a permanent cure, and improvement was probably spontaneous. It is probable that cures have been attributed to removal of focal sepsis in many patients because follow up was too short to reveal the true incidence of recurrence.

► [A difficult therapeutic problem regardless of diagnosis or etiology. In our experience too, removal of foci of infection (when found) is not satisfactory management of these annoying eruptions. Antibiotics, corticosteroids and other chemotherapeutic agents systemically and tar preparations topically, however, are well worth a trial.—Eds.]

Subcorneal Pustular Dermatosis. I. B. Sneddon and D. S. Wilkinson[2] report 6 cases of an uncommon dermatosis occurring mostly in middle-aged women and lasting from 3 months to 9 years. The axillae, groins, abdomen and flexor aspects of the proximal parts of the extremities were particularly affected. The hands, feet, face and mucous membranes were spared.

The individual lesions consist of pustules or vesicles which rapidly become pustular, flaccid, turbid and often oval in shape. Within a few days the pustules rupture, leaving a crust or scale. Pustules tend to form groups of annular or gyrate shape (Fig. 16), with an actively spreading edge. A reddish stain or brown pigmentation is left after healing. Atrophy does not occur. In successive attacks the same area of skin may be completely involved and further spread may occur at the periphery, or isolated groups of pustules may form within pigmented areas and die before spreading. The eruption has phases of alternate quiescence and activity lasting a few weeks as a rule, although in some cases the skin is al

(2) Brit. J. Derm. 68: 385-394, December, 1956.

most continuously affected by successive waves of pustules. Itching is moderate or absent. Blood studies were negative. The constant histologic feature is a subcorneal blister filled with polymorphonuclear leukocytes. Epidermal changes such as acantholysis are absent. Local or systemic treatment with antibiotics does not influence the eruption. Diamino-



Fig. 16. Pustules in groups of annular or gyrate shape with active spreading edge. (Courtesy of Sneddon, I. B. and Wilkinson, D. S.: Brit. J. Dermat. 68: 38, 194, December 1956.)

diphenyl sulfone (Dapsone) proved effective in 3 and partly successful in 1 of 5 patients.

In its protracted course, morphology and response to Dapsone, subcorneal pustular dermatosis resembles dermatitis herpetiformis. However, itching is not a prominent feature. The distribution is predominantly flexural and the histologic picture different. In impetigo herpetiformis, the general health is always affected, the mucous membranes are often involved and the histologic changes are unlike those seen in subcorneal pustular dermatosis.

Although the blisters are similar to those seen in impetigo contagiosa, an infectious basis for the eruption can be excluded by the clinical features, protracted course and complete fail

ure of the patient to respond to antibiotic treatment. The peculiar distribution of the eruption and its response to sulfone therapy tend to rule out any form of parapsoriasis.

► [As is pointed out by Sneddon and Wilkinson, the clinical features and the response to Dapsone suggest a relation to dermatitis herpetiformis. Until more cases have been studied, the question of whether subcorneal pustular dermatosis should be considered a separate entity cannot be answered.—Eds.]

Generalized Pustular Bacterid Its Relation to Pustular Dermatosis of Sneddon and Wilkinson was studied by F F Hellier[1] (Gen'l Infirm Leeds)

Man, 54 had a typical pustular bacterid on the palms and soles. Treatment with sulfathiazole, local applications and x rays produced little benefit. Six years later while the palmar and plantar lesions were still present, an eruption appeared on the trunk. These lesions

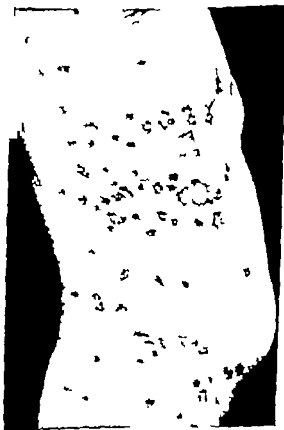


Fig 17—Lesions showing pustules border and scattered about unruptured but even larger patches (Courtesy F F Hellier F F Brit J Derma 68 395-399 December 1956.)

(1) Brit. J Dermat. 68 395-399 December 1956.

were circinate and guttate scaling erythematous patches. Active pustules were present at the borders and scattered between the larger patches (Fig 17) Lesions were also present on the extremities especially over the elbows. The genitals and mucous membranes were not affected.

Biopsy showed circular spaces filled with polymorphonuclears lying just under the horny layer Acantholysis was absent but there was spongiosis immediately below the pustules. The dermis showed a slight perivascular round cell infiltration.

There was no response to chlortetracycline, but the old lesions cleared rapidly with sulfapyridine. The patient could not tolerate the latter drug, however and showed no response to other types of treatment during the next 2 years. Dapsone was then given and the skin, including the palms and soles, cleared within 8 days. Subsequent relapses have been quickly suppressed by a few days' treatment with this drug

The trunk lesions resembled those described by Sneddon and Wilkinson as subcorneal pustular dermatosis. The microscopic picture was identical and the present patient, as well as those described by Sneddon and Wilkinson failed to respond to any treatment until Dapsone was administered. The author believes that the trunk eruption was the same as that on the hands and feet, since in both the pustules were intraepidermal, waxed and waned together and responded to the same treatment after resisting other forms of therapy The lesions on the palms and soles were typical of a pustular bacterid. He further believes that the lesions described by Sneddon and Wilkinson are the same disorder but because they appear in an uncommon site they assume a somewhat different character

► [Sneddon and Wilkinson make a point of the fact that the hands and feet—the characteristic sites of involvement in pustular bacterid—were spared in their cases of subcorneal pustular dermatosis.—Ed.]

Recurring Amicrobial Thoracic Pustulosis Duhring's Disease? Sneddon-Wilkinson Disease? B Duperrat (Paris) reports an interesting case.

Woman, 41 previously healthy had had recurring skin affection for 4 years. Eruption was first localized in the right iliac region, on trunk and thighs, sparing face, scalp extremities and mucosa. Each episode began with hundreds of pustular lesions (Fig 18) measuring 1 mm. to over 1 cm., slightly elevated, not umbilicated, not surrounding a hair containing a white opaque fluid and situated on an erythematous base with progressively enlarging contours. Lesions were sometimes isolated, sometimes confluent, sometimes in clusters. Around a drying primary pustule appeared a corona of smaller ones. In 3 or 4 days, pustules were covered with a slightly adherent yellow

( ) Ann dermat et syph. 84 5 4 132, Sept-Oct 1957

ish crust, which when it dropped off left a red macule, resembling chamois, that later disappeared completely without a scar. Attacks lasted 2-3 weeks, with remissions of 4-6 weeks. In each attack, successive waves resulted in marked polymorphism of lesions. Pronounced itching preceded the eruption by several days and became



Fig. 18. (Courtesy of Duperrat, B. Ann. dermat. et syph. 84:514-522 Sept.-Oct. 1957.)

maximal preventing sleep during the attack. General health remained good and temperature never exceeded 99.3 F.

Multiple bacteriologic and mycologic examinations, including animal inoculations, on fluid from the pustules were negative. Red blood cell count was 4,000,000; leukocyte count did not exceed 10,800, with 72% polymorphonuclear neutrophils; no eosinophils. Sedimentation rate was 35-62-115. Repeated biopsies showed a superficial subcorneal pustule.

Sulfapyridine was the only drug that afforded relief, but the initial excellent effect was lost after several weeks. Cortisone was then administered continuously for a year. The itch decreased considerably and attacks were less frequent and less severe.

At first, diagnosis of dermatitis herpetiformis seemed logical because of the general appearance of the eruption, coronal distribution of small pustules around a larger one, thoracic localization, absence of lymphangitis and adenitis, intermittent attacks intense pruritus, absence of fever preservation of general health and effect of sulfapyridine Duhring (1884) insisted on pre- or co-existence of vesicular bullous and pustular lesions In this case the eruption was solely pustular

Sneddon and Wilkinson described 7 patients with subcorneal pustular dermatosis, all but 1 middle-aged women. Eruptions on trunk axillas, loins and thighs appeared in attacks through several years without affecting the general health. Isolated, grouped or circular distribution of pustules was associated with dry crusting leaving brownish red pigmentation without atrophy Pus was sterile or contained staphylococci, never Candida albicans. Histologic findings were similar to those in the author s patient. A sulfone Dapsone had spectacular but transitory effect.

Probably the autho s case should be classified with the entity described by Sneddon and Wilkinson. The only dissimular featur was striking intensity of pruritus which originally oriented th diagnosis toward Duhring s disease.

Experimental Studies on Etiology of Pemphigus and Dermatitis Herpetiformis Duhring are reported by Emil Meirowsky[3] (Nashville, Tenn.) Filtered fluid from bullae and filtrated serums of patients with pemphigus and dermatitis herpetiformis injected into the testes of rabbits caused severe orchitis The experiments were discontinued because acute orchitis developed in control animals (normal serum) also in the 8th or 9th passage. The healthy looking rabbits obviously harbored latent endogenous virus which was activated by experimental procedures

In experiments on the eyes of rabbits no latent viruses could be activated. In contrast with homologous and heterologous normal serums, filtered fluid from bullae or filtered serum from patients with pemphigus or dermatitis herpetiformis when injected between lamellae of the cornea or into the anterior chamber of the eye, produced long lasting keratitis interstitialis, with separation of epithelium and substantia propria corneae and even bulla formation. Occa

(3) Nature 159 [illegible], September 1947

sionally iritis scleritis or conjunctivitis occurred with interstitial keratitis Clinically and microscopically interstitial keratitis so produced corresponded to the manifestations of patients with pemphigus or dermatitis herpetiformis. Injection of inactivated serums or fluid from bullae of patients with pemphigus or dermatitis herpetiformis caused only subepithelial aggregations of infiltrating cells never massive deep infiltration of the entire cornea.

Experiments with filtered serums or fluid from bullae dropped onto the chorioallantois and yolk sac membranes of hatched chicken eggs resulted in formation of an enormous, long lasting infiltrate consisting of lymphocytes mesenchymal cells and a moderate amount of eosinophils Intravenous injection of 0 02-0 05 cc filtered fluid from bullae or serums from patients with pemphigus into the large chorioallantoic vein was usually followed by death of embryos within the eggshell Fully hatched surviving chickens became paretic, lost ability to move and drink finally lay apathetically on the belly with straddled legs and toes and died between 1 and 10 days (neurologic deficit)

Electron microscopy of fluid from bullae from patients with pemphigus or dermatitis herpetiformis revealed "virus-like particles the dimension of which were those of true viruses Particles from pemphigus bullae showed an average length of 20-50 mμ, width of 20-40 mμ and height of 15-30 mμ particles from dermatitis herpetiformis Duhring varied between 60 and 85 mμ.

Despite positive results which support the hypothetic viral etiology of pemphigus and dermatitis herpetiformis further experimental research work is required e.g., the promising method elaborated by Goodpasture and associates of transfer of human material (kin of children and adults fetal membranes) which before and after transplantation onto the chorioallantois of hatched chicken eggs was inoculated with virus material On the assumption that antibodies are formed in the serum of patients with pemphigus or dermatitis herpetiformis Duhring it would be interesting to investigate whether the addition of such antibodies to the inoculum would prevent development of the pathologic changes

Senear Usher Syndrome Review of Literature and Own Observations are presented by J Tappeiner and P Wodni

ansky (Uni of Vienna) Probably the most suitable name for the syndrom is pemphigus erythematosus. It is characterized by a triad of lupus erythematosus-like lesions on the face, changes related to eczema seborrheicum and vesicular eruptions. The disease affects both sexes equally and is commonest in middle age At first, symmetrical erythematous lesions, covered by fatty scales occur on both cheeks the forehead and ears. In 1 patient, the first lesion appeared on the



Fig 19 —Symmetric crusty lesions with eruptions on face and scalp in pemphigus erythematosus (Courtesy of Tappeiner J and Wodniansky P Arch klin u exper Dermat 207 . . . 1, 25)[?])

scalp and the face was spared during the whole course of the disease.

Besides the seborrheic component, lesions on the face and scalp may present exudative changes leading to thick scales similar to impetigo contagiosa (Fig 19) Later seborrheic and bullous eruptions spread over the whole trunk but rarely reach the extremities. The vesicles are occasionally accompanied by itching are loose, filled with serum and short lived. The fresh vesicles are surrounded by the various lesions developing from burst vesicles. These vesicles are very similar to the fleeting blisters of pemphigus follaceus but in

(4) Arch. klin. u exper Dermat 207:141 145, 1957

the latter the blisters often become generalized. The Nikolski phenomenon is positive in both diseases

None of the patients had mucosal lesions. Prolonged, continuous cortisone treatment effectively suppressed the lesions. One patient who became asymptomatic had remained so for 3 years Differential diagnosis includes lupus erythematosus impetigo contagiosa eczema seborrheicum, psoriasis vulgaris erythema exudativum multiforme, dermatitis herpetiformis atypical lichen ruber planus bullosus and epidermolysis bullosa.

It is believed that pemphigus erythematosus is not a variant of lupus erythematosus but belongs to the disease group of pemphigus. This is in accordance with observations that the disease may eventually turn into malignant pemphigus furthermore the histologic picture is identical with that of pemphigus foliaceus That pemphigus vulgaris can, under the influence of cortisone change to pemphigus erythematosus as in 2 of the patients speaks for the assumption that both diseases are the expression of basically the same pathologic process

Benign Pemphigoid? Report of Seven Cases with Chronic, Scarring Herpetiform Plaques about Head and Neck is presented by Louis A Brunsting and Harold O Perry[7] (Mayo Clinic and Found) All but 1 patient were men The eruption consisted of grouped pruritic vesicles confined to one or more circumscribed plaques on the head and neck. The course extended over a period of years and was characterized by a succession of flares Scarring of the affected sites occurred. In 2 instances brief episodes of vesicular exanthems occurred (Fig 20) In 1 patient lesions appeared in the mouth and pharynx and later on the conjunctivae but in all others, only the skin was involved Allergic incidents particularly urticaria and asthma, occurred in most patients

The process was persistent but essentially benign. This is borne out by the microscopic findings which show absence of acantholysis and localization of the bullae at the subepidermal level Eosinophils predominate in the dense cellular infiltrate. Except for scarring the clinical features suggest a localized form of dermatitis herpetiformis but the patients were not sensitive to iodides and responded only irregularly to sulfapyridine or arsenic The primary plaque of true pem-

(7) A.M.A. Arch. Dermat. 75 489-501 April, 1957

phigus vulgaris, as well as chronic benign familial pemphigus, deserves passing attention Other conditions to be considered are recurrent herpes simplex, bullous lupus erythematosus, bullous lichen planus factitial dermatitis l ght



Fig 58.—Vesicular [illegible] at [illegible]. (Courtesy of Brunsting, L. A and Perry H O A M A Arch. Dermat. 75 489 [illegible] April, 1957)

sensitivity such as porphyria, fixed eruptions and ben gn mucosal pemphigoid.

Blistering with scarring may be one of the rare cutaneous manifestations f so-called ocular pemphigus or benign mucosal pemphigoid. In this series, 1 patient had mouth, pharynx, and conjunctival lesions. However in the authors experience the peculiar cutaneous pattern seen in the present cases has not been observed in ocular pemphigus.

Herpes Gestationis is reported by Brian Russell and V A Thorne[8] in 11 cases seen at the London Hospital during 1921 55 Incidence was 1 in 3 000+ deliveries Onset was in the 8th or 9th week of gestation in 2 pregnancies, between the 12th and 24th weeks in 13 between the 25th and 40th weeks in 7 and during the first 3 days of the puerperium in 5 Once herpes gestationis occurred it recurred in all subsequent pregnancies Onset in the puerperium was followed by onset during gestation in all later pregnancies repeated onset during the puerperium did not occur

In 8 patients tendency toward remission was noted during the last few weeks of pregnancy In 7 time of remission was not stated and 7 showed no remission Recrudescence occurred on the 1st 3d day of the puerperium in 10 no recrudescence occurred in 6 and the record was incomplete in 6 The eruption cleared in 4 weeks after delivery in 6, in 8 weeks in 7 in 12 weeks in 4 and in 16 weeks in 1 In 9 time of final clearing was not stated.

In 9 the eruption developed centripetally in 2 development was sometimes centripetal sometimes centrifugal In 2 the mucosae was involved Blood eosinophilia was 5-10% in 3 11 15% in 2 16-20% in 1 21 25% in 2 and 25-30% in 1 Response to treatment with liquor arsenicalis was doubtful or absent in 3 Response to sulfapyridine was doubtful or absent in 3 and moderate in 1 With progesterone results were good in 1 doubtful in 1 and bad in 1 Results were good in 3 with cortisone or ACTH

The exciting cause of herpes gestationis appears to be an abnormal metabolic or endocrine product of pregnancy the puerperium and the premenstrual phase The natural history suggests that sensitization develops to this agent or that the agent is produced in excess is incompletely destroyed or is inadequately excreted Increased gonadotropins found in the blood and urine are unlikely to be of chorionic but may be of pituitary origin

Both herpes gestationis and dermatitis herpetiformis are extensive exceedingly pruritic bullous eruptions with histologic identity and eosinophilia In the former spread is usually centripetal whereas in the latter either centripetal or centrifugal spread is unusual The lesions of herpes gestationis are often polycyclic which is rare in dermatitis

(8) Brit. J Dermat. 69 339 357 October 1957

herpetiformis. Dermatitis herpetiformis shows a predilection for the shoulders, buttocks, elbows and knees. In herpes gestationis, excoriation is slight and scarring and pigmentation minimal, whereas in dermatitis herpetiformis excoriation, scarring and pigmentation are often pronounced. Oral lesions may occur in the former but not in the latter. In herpes gestationis, Dapsone and sulfapyridine are usually ineffective and estrogens may aggravate and progesterone may relieve symptoms. In dermatitis herpetiformis, Dapsone and sulfapyridine usually suppress the lesions and itching, but estrogens and progesterone are ineffective.

At present cortisone is the best drug for controlling herpes gestationis and is safe for mother and infant provided use is limited to the 2d trimester and the earlier part of the 3d trimester. Fortunately it is not necessary to give steroid hormones early in pregnancy because herpes gestationis rarely appears before the 2d trimester. Since the intensity of the eruption often tends to diminish toward the end of pregnancy it is usually possible to reduce the dosage and finally withdraw the drug 1 or 2 weeks before term. Postpartum exacerbations can be treated safely with cortisone.

► [In exceptional cases, herpes gestationis continues for many months after delivery. In one such patient under our observation, cortisone was the only drug which relieved the persistent bullous eruption and associated severe itching.—Eds.]

Stevens-Johnson Syndrome: Report of Five Cases and Discussion on Etiology and Treatment are presented by Ian A. Short[9] (Manchester Royal Infirm.). Two patients died, 1 of atypical pneumonia. At autopsy the other showed lesions of polyarteritis nodosa in the testes, skeletal muscles, myocardium and peripheral nerves. Fibrinoid necrosis of the capillaries was found in the lungs and fibrinoid necrosis of trabecular arteries in the spleen.

A very critical approach should be made in attributing cases of Stevens-Johnson syndrome to drug allergy. The first patient received no sulfonamides or other probable allergen, the second only thiouracil. The third seemed to improve when sulfonamides were administered during an attack, and the fourth received no potentially sensitizing drugs. In the fifth, the disease might have resulted from sulfonamides, but the time relation makes this unlikely. Sore throat, painful eyes and skin eruption appeared 1 week after a 4-day

(9) Lancet 1:294, Feb. 9, 1957.

course of sulfadimidine for cystitis It seems probable that the infections for which the various antibacterial agents were given could be the precipitating cause of the syndrome.

Chlortetracycline and chloramphenicol have been said to produce improvement in some cases but were not helpful in the 2 patients who died However both were desperately ill when treatment was begun Cortisone and ACTH are reported to cure the syndrome and this is adduced as further evidence of an allergic basis for the condition. It is not certain however that the antiallergic properties of these drug are responsible for the cures Possibly many instances of improvement are due to spontaneous remission Short concludes that the cause of Stevens Johnson syndrome remains obscure

► [It is not unusual that the beneficial results which follow treatment with corticosteroids or ACTH are attributed to the antiallergic effects of these drugs. On that basis one would have to draw the presumably erroneous conclusion that diseases such as pemphigus, alopecia areata and totalis and certain forms of shock which are benefited by corticosteroids and ACTH are produced by an allergic mechanism. This seems hardly justified since such a conclusion disregards the many other effects of these hormonal agents.—Eds.]

Stevens Johnson Syndrome According to modern concepts this syndrome is identified with ectodermosis erosiva pluriorificialis dermatostomatitis conjunctivitis et stomatitis pseudomembranacea mucosal respiratory syndrome and acute mucocutaneo-ocular syndrome. Because of similarities with and relations to erythema exudativum multiforme Hebra (EEMH) it is denoted as the erythema exudativum multiforme syndrome (EEMS) There is an increasing tendency to consider EEMS as grave type of EEMH and, with American authors to unite both in one entity as multiform erythema," the etiology of which is still obscure. P Jordan R. Burckhardt and Th Nasemann[1] (Univ of Munich) report a case of Stevens Johnson syndrome in an attempt to clarify the etiology and relations to viral diseases

Man, 22 after uncharacteristic initial symptoms showed quickly rising temperature, rheumatoid pains and from the 3rd day on multiform ex and enanthema which with continued fever persisted over 2½ weeks, leaving brownish macules. Subfebrile temperatures continued for 4 more weeks, with marked weakness. He showed enlarged spleen, cystitis mitral endocarditis and myocarditis. Hemogram revealed leukopenia with lymphoreticulary and monocytic reaction. Changes of serum proteins and erythrocite sedimentation rate were most marked in the 6th week. X ray examination of lungs was nega

(1) Arch. klin. u. exper. Dermat. 204 604 623 1957

th A systolic murmur over the pex cordis, and transitory changes in the ECG were noted. Salicylates and penicill were ineffective, but spontaneous remissions occurred.

The liquid content and small particles of fresh vesicular lesions, nasal discharge, sputum, enoos and sternal blood were investigated between the 6th and 11th day Unstained and stained smears for elementary bodies were examined with the light phase- and electron microscope. Inoculations of chorioallantoic membrane and cornea of rabbits were made and examined in the same way and venous and sternal blood was administered intracerebrally into white mice and intraperitoneally into guinea pigs and checked as described above. All experimental investigations failed. Elementary bodies were not found in smears, corneal tests were not followed by keratiti or conjunctiv tis of animals, intracerebrally infected white mice survived and no elementary or inclusion bodies were found in inoculated chorioallantoic membranes

These negative result do not ju tify exclusion of a virus etiology especially as review of the literature reveals that a irus may be the etiologic agent The fever curve, which in EEMS often shows a depression on the 3d or 4th day resembles the dromedary curve seen in some virus diseases. Respiratory nfections observed in EEMH and EEMS inlud bronchitis and pneumonia the latter u ually being ba terial or primary typical pneumonia. Inclus on occasionally found in sputum cells of primary atypical pneumonia correspond morphologically to inclusion bodies produced in rabbit cornea by inoculation of material from EEMS. Association of herpes simplex nd EEMS and EEMH ha often been reported, with the herpetic infection preceding follow ing or coexisting in the patient or in person in the environment. M ltiform erythemas were also seen to f llow other iral infections, e g arıola, vaccination, milkers nodes, lymphogran loma nguinale, parotitis, poliomyelitis.

Although no specific virus could be isolated, the authors conclude that, possibly via the reticuloendothelial system, various agents may cause allergic-hyperergic reactions (mi crobids viruside") with gradually different, morphologically consistent man festations.

Cutaneous and Severe Ungual Symptoms in Urethroconjunctivosynovial Syndrome were observed by E Gri eaud, J Achard a d J Marchetx

Youth, 19 had subacute urethritis, with intestinal symptoms that lasted few days at onset. Despite penicillin-streptomycin treatment, conjunctivitis and severe painful swelling of the joints appeared 12 days after urethritis Three week later conjunctivitis had regressed

(2) Ann dermat et syph 84 466-465 July Aug 195

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(1) Arch. klin. u. exper Dermat 204 604-623, 1957

showed acanthosis with elongation of interpapillary buds. Bacteriologic and viral studies of material removed from the anterior chamber revealed no sign of infection. With large doses of prednisolone (1 drop every hour) and 1 injection of Irgapyrine /day hypopyon and exudate in anterior chamber cleared completely in 2 days.

In view of Kornblith's (1944) success in preparing an antigen from lesions of granuloma inguinale which yielded positive intradermal reactions in the patient, a similar procedure was tried. A scrotal specimen 1×0.5 cm was sectioned and kept in 1 cc. physiologic saline at about 4 C. and was sterilized (tyndallized) intermittently 1 hour/day for 4 days. Before the last sterilization fluid was filtered through paper.

Injections of 0.1 cc. of this antigen were given intradermally to the patient and to 3 controls who had never had aphthous lesions. After 24 hours, the patient showed a red infiltrated reaction about 10 mm. in diameter; after 48 hours this was surrounded by a red halo of about 2.5 cm., and after 72 hours, the reaction was still slightly positive. In all controls, reaction was negative after 24 and 48 hours, and it was hard to determine where the injection had been made.

Thus, the patient with Behçet's syndrome showed a reaction of tuberculin type (delayed reaction) with an antigen prepared from a noninfected scrotal lesion. In view of its theoretical interest and the rarity of Behçet's syndrome, it seems worth while to report this single case with the hope that other investigators will confirm it.

► [As was pointed out to us by W. Jadassohn (personal communication) it remains to be seen whether this is a specific reaction. The development of a specific skin test for Behçet's disease would be of great aid in establishing the diagnosis and could be strong evidence in favor of an infectious (viral) etiology in this disease.—Eds.]

Encephalomyelopathy in Behçet's Disease: Report of Necropsy Findings in Two Cases is presented by W. H. McMenemey (London) and Beryl J. Lawrence (Hollywood, Western Australia). The first patient, besides the usual symptoms and signs of Behçet's disease, had frequent convulsions and spastic paraplegia. The second had mental deterioration, nystagmus, tetraparesis, dysarthria and dysphagia. A virus was isolated from a mixture of cerebrospinal fluid and white matter. At autopsy in both cases the central nervous system lesions were multiple with a distinctive pattern of predilection for the hypothalamus and brain stem.

Lancet 355-358, Aug. 24, 1957

but the joint condition remained unchanged. Pustules, 2-4 mm. in diameter with an erythematous halo appeared on the buttocks, pretibial areas and elbows. A few days later identical lesions occurred on fingers and toes, except the left thumb and little finger especially at digitopalmar folds and points of plantar pressure. The pustular stage was short (48 hours) and was replaced by keratotic formations, 6-7 cm. in diameter. During this period, heart sounds were muffled, without valvular blowing or rhythmic changes. The articular condition was stationary and temperature ranged from 100.4 to 101.3 F.

On examination 2 months after onset of urethritis, topography and appearance of skin lesions on elbows, forearms and knees resembled psoriasis. There were hard horny palmar and keratotic plantar lesions, with a thick translucent covering which could be easily lifted, revealing a red, raw sensitive surface, which was shiny, oily and painful especially on the edge. Ungual lesions were striking. Some nails looked as if mounted in a fluted ruff: a festooned keratotic pad which developed, according to the patient, within hours, on drying of the garland of pustules in the nail groove and soft tissue under the free edge. The lunula was sometimes involved, but the ungual plate only slightly. The free edge was thinned, whitish and detached, being raised by a thick soft waxy yellowish bed, which could be easily lifted, uncovering pale red tissue with small craters, apparently corresponding to the primary pustules.

For 2 months, the patient had received various types of medication, including penicillin, streptomycin and salicylates intravenously and typhomycin, tetrasulfamide oxytetracycline and hydrocortisone by mouth without appreciable results. After medication was suspended for 4 days, 1 Gm. chlortetracycline/day resulted in rapid improvement in the joint condition (5 days) and cutaneous manifestations which had practically disappeared after 10-15 days. Ungual and periungual lesions regressed more slowly. Five nails were totally lost.

Re-examination 4 months later showed that general condition was excellent, with no joint sequelae, normal skin free from scars and complete regeneration of nails, which showed no abnormality.

► [The clinical description of this disease fits the picture of Reiter's syndrome. Foxworthy and associates (Am. J. M. Med. 44:52, 1956) reported that benefit in this condition was derived from ACTH and cortisone. When evaluating therapy in Reiter's disease it must be kept in mind that spontaneous improvement is not uncommon.—Eds.]

Cutaneous Reaction in Case of Aphthous Uveitis with Recurring Hypopyon (Behçet's Syndrome) to an autogenous antigen is reported by W. Jadassohn, A. Franceschetti and M. Golay[3] (Univ. of Geneva). Besides the recurring ocular lesion the patient also had small thrushlike buccal lesions and nonulcerated red patches on the scrotum. Histologically these patches showed nonspecific dermatitis with perivascular lymphohistiocytic infiltrate in all dermal layers predominantly in the papillary layer. Subjacent epidermis

(3) Schweiz. med. Wchnschr. 87:1188, Sept. 21, 1957.

Biopsy of a rib showed typical eosinophilic granulomas of the bone. Skin biopsy showed a patchy cellular infiltration of mast cells and histiocytes in the upper dermis. No eosinophils were noted.

Few cases of nonlipid reticuloendotheliosis (Letterer Siwe disease) have been reported in adults The histologic changes in the authors case resemble those found in Letterer Siwe disease in infants but the clinical course was prolonged. This case combines some of the features of several diseases seen in children The skin lesions correspond clinically and histologically to those of Letterer Siwe disease. The granulomatous histiocytic proliferation and lack of foam cells in the liver spleen and lymph nodes also resemble this disease even though prominence of eosinophils in the lymph nodes and liver suggest Hand-Schuller-Christian disease The widespread bone lesions are typical of eosinophilic granuloma in younger persons. There is little resemblance to histiocytic medullary reticulosis, particularly clinically The prolonged course is unlike Letterer Siwe disease and does not suggest relation to the malignant reticuloendothelioses

Cutaneous Manifestations of Letterer-Siwe Disease. Donald M Rueh (Milwaukee) reports 4 cases of Letterer Siwe disease (malignant histiocytoma) The condition a rare nonlipoid reticuloendotheliosis, usually fatal occurs oftenest in children under age 2 Splenomegaly hepatomegaly and lymphadenopathy are usually present Most patients have low-grade hypoplastic anemia. X-rays of the bones may reveal cystic lesions and chest x rays may show nodular infiltration of the lungs simulating tuberculosis

The skin lesions oftenest seen are red scaly and papular are mostly on the scalp face and neck and simulate seborrheic dermatitis. A second group of lesions consisting of vesicles and vesiculopustules may be present and resemble trichophytosis or moniliasis. Petechiae, eczematoid reactions and exfoliation occasionally occur Two patients showed purpuric and petechial lesions and 1 showed cutaneous nodules and ulcerative lesions with vesiculopustules and scaly dermatitis

The distinctive pathologic feature of Letterer Siwe disease is a nodular profuse proliferation of histiocytes in the skin liver spleen lymph nodes and sometimes in skeletal and pulmonary tissue The cells are nonlipid-storing large, round or polygonal mononuclear cells The cytoplasm is pale stain

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[40] A M A Arch Dermat 75 88 93, January 1957

They consisted of innumerable small softenings in relation to the smaller blood vessels and were seen oftener in white matter than in gray. Inflammatory reaction was seldom obvious and myelin loss appeared to be secondary.

The relapsing character of Behçet's disease and the pathologic findings might suggest that the mechanism of the brain disease is allergic in nature. However, if the virus isolated from cerebrospinal fluid and white matter in the second patient is accepted as the cause of the disease, it could be responsible for the lesions by direct involvement. The individual neurologic episodes could be explained on the basis of recurrent viremic phases, the paucity of inflammatory cells being attributed to the chronicity of the infection.

Nonlipid Reticuloendotheliosis in Adult. Report of Case, presented by Dale M. Schulz, George B. Hamilton and Leton B. Nay.[3]

Man, 57, in 1956 was admitted to Valley Forge Army Hospital because of weakness, lassitude and weight loss for 2 years. He had an eruption, first apparent about 10 years previously, on the chest and back and to a lesser extent on the arms and legs, which consisted of discrete maculopapules, 2-4 mm. in diameter, and larger confluent areas. The lesions blanched on pressure, but some hyperpigmentation remained.

On hospitalization in 1955, examination disclosed ascites, enlarged liver and generalized enlargement of lymph nodes, and laboratory tests showed peripheral eosinophilia of 10%, sedimentation rate 26 mm./hour, thymol turbidity 10 units, bromsulfalein retention 12%, serum alkaline phosphatase levels 20 S. J. R. units and total serum protein levels 6.2 Gm./100 ml. with albumin-globulin ratio 2.4:2. Exploratory laparotomy revealed ascites, nodular enlargement of liver, generalized enlargement of mesenteric lymph nodes and a penetrating duodenal ulcer. Partial gastrectomy was performed, and he did well postoperatively. Biopsy of liver, spleen and lymph nodes was done at time of surgery. The liver showed focal replacement of hepatic cells by whorled masses of histiocytes, a few lymphocytes and varying numbers of eosinophils. The spleen showed sparse infiltration of lymphocytes, histiocytes and few eosinophils. The lymph nodes contained whorled masses of histiocytes with scattered reticulum cells and lymphocytes and a moderate number of eosinophils. Microscopically, there was striking eosinophilic and histiocytic infiltration around the chronic duodenal ulcer.

During the present hospitalization he was placed on a high-vitamin, high-calorie diet, with use of intravenous salt free albumin. Liver function gradually returned to near normal and he was symptomatically improved. Bone x-ray study revealed widespread, spotty demineralization of bones with finely trabeculated cystic areas, especially in the pelvis, ribs, upper extremities and heads of the clavicles.

(3) A. M. A. Arch. Path. 63: 49-54 (January) 1957.

Biopsy of a rib showed typical eosinophilic granulomas of the bone. Skin biopsy showed a patchy cellular infiltration of mast cells and histiocytes in the upper dermis N eosinophils were noted.

Few cases of nonlipid reticuloendotheliosis (Letterer S we disease) have been reported in adults. The histologic changes in the authors case resemble those found in Letterer S we disease in infants, but the clinical course was prolonged. The case combines some of the features of several disea es seen n children. The skin lesions correspond clinically and histologically to those of Letterer Siwe disease. The gran ulomatous histiocytic prol feration and lack of foam cells in the liver spleen and lymph nodes also resemble this d s-ease, even though prominence of eosinophils in the lymph nodes nd l er suggest Hand Schüller-Christian disease The widespread bone lesions are typ cal of eosinophilic gran uloma in younger persons. There is little resemblance to histiocytic medullary reticulosis, particularly clinically The prolonged course is unlike Letterer Siwe disease and does not suggest a relation to the malignant reticuloendothelioses.

Cutaneous Manifestations of Letterer Siwe Disease. Donald M Ruch[4] (M lwaukee) reports 4 cases of Letterer Siwe disease (malignant histiocytoma) The condition, a rare non lipoid eticuloendotheliosis, usually fatal occurs oftenest n child en u der age 2 Splenomegaly hepatomegaly and lymphadenopathy are usually present. Most patients ha e low-grade hypoplastic anemia X rays of the bones may re veal cystic lesions and hest x-rays may how nodular infil-tration f the lungs simulati g tuberculosis.

The skin lesions oftenest seen are red, scaly and papular are mostly on the scalp face and neck and simulate sebo rrheic dermatiti A second group of lesions cons sting of esicles and es culopustules may be present and resembl trichophytosi or monilia s. Petechiae, eczematoid reactions and exfoliation occasionally occur Two patients showed purpuric and pete hial lesions and 1 showed cutaneous nod les a d ulcerativ lesions with esiculopustular and scaly dermatitis.

The di tinctive pathologi feature of Letterer Siwe disease is nodular profuse prol feration of histiocytes in the skin, li er pleen lymph nodes and sometimes in skeletal and pulmonary tissue. The cell are nonlipid-storing large, round or polygonal mononuclea cells. The cytoplasm is pale stain

4) A.M.A. Arch Dermat 75 [illegible] January 1957

ing the nucleus is usually chromatic often eccentrically situated, sometimes vesicular and sometimes more oval or spindle-shaped. Sternal puncture reveals hyperplastic bone marrow

Treatment is unsatisfactory but antibiotics steroids, splenectomy and radiation therapy of the bones may prolong life.

Cutaneous Manifestations of Letterer-Siwe Disease. John M Reichert[7] reports 2 cases Letterer Siwe disease is an acute generalized disease of the reticuloendothelial system that typically occurs in infants and ends fatally in weeks to months. The cause is unknown In the classic case, there is pronounced hepatosplenomegaly enlargement of the lymph

[illegible] hemorrhage [illegible]

filtration of the spleen liver lymph nodes, bone marrow skin thymus and other organs with these cells which contain little or no lipid material.

Not all patients show the classic signs and symptoms. A skin rash often is the first sign of illness, and as the disease progresses the rash may become quite striking The cutaneous lesions are essentially areas of small or large hemorrhage into the skin The basic skin lesion usually is overlaid by an eczematoid reaction or infection of the skin or both, so that recognition of the hemorrhagic nature of the original lesion may be difficult, but careful examination will reveal the hemorrhage beneath the associated eczema or infection.

Boy aged 9 months, with extensive skin eruption for 6 months, had the scalp covered by infected seborrheic eczema. The chest, abdomen and back were involved with scaling papulopustular eruption. The skin appeared red and raw (Fig 21) Many petechiae were noted, scattered over the entire trunk and partially obscured by the overlying dermatitis. The posterior cervical and inguinal lymph nodes were large firm and questionably tender The liver was enlarged but the spleen was not palpable. Hemoglobin value was 11 Gm./100 ml red blood cell count 3,800 000 and white blood cell count 9,350/cu. mm., with differential normal.

Three months later rather sudden deterioration in the condition occurred. He had fever respiratory distress and more extensive skin eruption. Chest x ray study showed fibrosis in both lung fields. The spleen was enlarged. Respiratory effort increased the rash became worse and he died at age 13 months. Autopsy revealed extensive diffuse infiltration of both lungs with large reticuloendothelial-like macrophages. The skin showed extensive infiltration of the same

(7) Quart. Bull. North western Univ. M. School 31 37 39 Spring, 1957

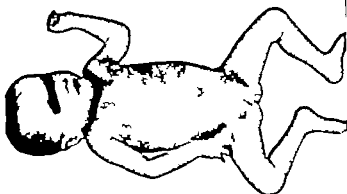


Fig. 21.—Rash of Letterer-Siwe disease. (Courtesy of Rabbert, J. M.: Quart. Bull. Northwestern Univ. M. School 31:37-39, Spring, 1957.)

macrophages in the upper layers of the dermis and the lower layers of the epidermis. The spleen, liver and lymph nodes also were extensively infiltrated with broad sheets of the same cells. Diagnosis was nonlipid histiocytosis (Letterer-Siwe disease).

► [The clinical picture of Letterer-Siwe disease is not always typical. When there is widespread eczematous eruption in an infant who appears systemically ill, this disease should be considered in the differential diagnosis.—Eds.]

Eosinophilic Granuloma of Skin and Mucous Membrane Association with Diabetes Insipidus is reported in 4 patients and only cutaneous features in a 5th by Robert B. Kierland, John G. Epstein and Walter E. Weber[8] (Mayo Clinic and Found.). Clinical changes in all were similar and consisted of deep, sharply delineated ulcerating granulomatous lesions of the skin of the inguinal, perianal, perineal and vulvar regions, the buccal mucous membrane and hard palate (Fig. 22). The last case, that of a girl, age 2, the only one without diabetes insipidus, had involvement of the vulva and not of the oral and anogenitocrural areas. The diagnosis of eosinophilic granuloma was made from biopsies and microscopic examination. Eczematoid seborrheic dermatitis occurred in 3 women, particularly in the inframammary region.

Therapy consisted of general supportive measures, anti-inflammatory applications and antibacterial regimens. Roentgen therapy was used specifically. One patient received corti

(8) A.M.A. Arch. Dermat. 75:45-54, January, 1957.

ing the nucleus is usually chromatic often eccentrically situated, sometimes vesicular and sometimes more oval or spindle-shaped Sternal puncture reveals hyperplastic bone marrow

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M Reichert[7] reports 2 cases Letterer Siwe disease is an acute generalized disease of the reticuloendothelial system that typically occurs in infants and ends fatally in weeks to months The cause is unknown In the classic case there is pronounced hepatosplenomegaly enlargement of the lymph nodes fever anemia, localized bone defects and hemorrhagic diathesis resulting in cutaneous hemorrhages. Histologically there is hyperplasia of reticuloendothelial cells and infiltration of the spleen liver lymph nodes bone marrow skin thymus and other organs with these cells, which contain little or no lipid material

Not all patients show the classic signs and symptoms. A skin rash often is the first sign of illness, and as the disease progresses the rash may become quite striking The cutaneous lesions are essentially areas of small or large hemorrhage into the skin The basic skin lesion usually is overlaid by an eczematoid reaction or infection of the skin or both, so that recognition of the hemorrhagic nature of the original lesion may be difficult but careful examination will reveal the hemorrhage beneath the associated eczema or infection.

Boy aged 9 months, with extensive skin eruption for 6 months, had the scalp covered by infected seborrheic eczema. The chest, abdomen and back were involved with scaling papulopustular eruption. The skin appeared red and raw (Fig 71) Many petechiae were noted, scattered over the entire trunk and partially obscured by the overlying dermatitis. The posterior cervical and inguinal lymph nodes were large firm and questionably tender The liver was enlarged but the spleen was not palpable. Hemoglobin value was 11 Gm./100 ml red blood cell count 3,800 000 and white blood cell count 9,350/cu. mm., with differential normal

Three months later rather sudden deterioration in the condition occurred. He had fever respiratory distress and more extensive skin eruption. Chest x ray study showed fibrosis in both lung fields. The spleen was enlarged. Respiratory effort increased, the rash became worse and he died at age 13 months Autopsy revealed extensive diffuse infiltration of both lungs with large reticuloendothelial-like macrophages. The skin showed exten e infiltration of the same

(7) Quart. Bull. Northwestern Univ. M School 31 37 39 Spring 1957

globulinemia. Clotting time was normal and prothrombin time reduced. There was marked increase of basophil granulocytes in the blood and mastocytosis of the skin but no evidence of leukemia.

Blood basophilia is an interesting finding with mastocytosis but does not indicate the origin of the mast cells. This case implies mast cell accumulation is essential to the clinical manifestations of urticaria pigmentosa. Without this accumulation the diagnosis is erroneous.

► [Roentgen ray examination of the bones did not reveal the osteosclerotic lesions described by Sagher and others but the bone marrow showed an excess of mast cells in all specimens examined.

In view of the role of the tissue mast cell in some species of animals in the metabolism of 5-hydroxytryptamine (serotonin), it would be interesting to do assays for this substance in the blood and for its metabolic product, 5-hydroxyindoleacetic acid, in the urine of all patients with urticaria pigmentosa.—Eds.]

Mast Cell Leukemia Presenting as Urticaria Pigmentosa. Report of Case is offered by William J. Waters and Perpetua S. Lacson (State Univ. of New York, Syracuse).

Boy, 5, with skin eruption and generalized lymphadenopathy since infancy, was hospitalized because of fever, lethargy and vomiting. For years the mother had noted easy bruisability and difficulty in arresting hemorrhage from minor cuts. Examination revealed generalized eruption with erythema, vesicles, excoriations, crusting and urticarial wheals. White dermatographism was easily elicited. There were petechiae in the conjunctiva and on the soft palate. The abdomen was distended and the liver and spleen were enlarged.

Hemoglobin was 10.2 Gm./100 ml., hematocrit 29%, leukocytes 11,000/cu. mm., neutrophils 46%, lymphocytes 51%, eosinophils 3%, platelets normal, bleeding time 6.5 minutes, clotting time 5 minutes, clot retraction normal, prothrombin time control 13 seconds and patient 2 minutes, and serum lipemic clearing factor was negative. About 25% of the nucleated cells in the sternal bone marrow were tissue mast cells. Tissue mast cell infiltration was noted in a skin and lymph node biopsy. Review of the peripheral blood smear showed a moderate number of tissue mast cells.

On the 3d hospital day he had abdominal pain and vomited. Respirations became labored, and he died. Autopsy showed a large amount of bloody fluid in the peritoneal cavity that had come from rupture of a large subcapsular hematoma of the liver. The blood was entirely fluid and had not clotted in the peritoneal cavity. The liver and spleen were extremely enlarged. An invasion of characteristic tissue mast cells was found in most of the organs, the liver being most massively involved. Its architecture was distorted, and liver cords appeared atrophied from pressure of the invading cells. Heparin and histamine determinations on frozen, postmortem specimens of liver showed concentration of about 100 times normal.

Although the tissue mast cell has been identified as the characteristic cell in the skin lesions of urticaria pigmentosa,

(Pediatrics 19:1033-1042, June, 1957)

sone with no benefit Another received triethylene melamine with excellent results Vasopressin was effective in controlling the diabetes insipidus of all 4 patients

Histologically the epidermis showed acanthosis, spongiosis and ulceration The dermal infiltrate was mostly large mononuclear cells with indistinct boundaries and indented nuclei Eosinophils were abundant Areas of pseudonecrosis



Fig. 22.—Granuloma of hard palate (Courtesy of Kierland, R. R., et al A M A Arch. Dermat. 75 45-54 January 1957)

were prominent in the ear hard palate and vulvar region, differentiating this condition from other eosinophilic infiltrations of the skin

Systemic Mast Cell Disease Involving Skin Liver Bone Marrow and Blood Associated with Disseminated Xanthomas. A case is reported by G Asboe Hansen and O Kaalund Jørgensen[8] (Copenhagen) Enlargement of the liver and spleen has been observed with urticaria pigmentosa which may be associated with systemic mastocytosis. Mastocytosis has not been known to be accompanied by alterations in fat metabolism or xanthomatosis

Man, 35 with white and yellow nodules for 1 year also showed many brown spots, some of which tended to be confluent Injury to the skin elicited urtication. Diagnosis of disseminated xanthomas and urticaria pigmentosa was made Bone marrow section and a liver biopsy specimen showed many mast cells with metachromatic granules. Blood lipids and heparin values were normal but there was hyper

(8) Acta dermat 16:373-379 1 56

many infiltrations of mast cells in the skin, organs and involved bones. Monocytic leukemia involved the parenchymal organs and reticuloendothelial system.

In both patients the bone lesions were dynamic and progressive. The x ray changes in urt caria pigmentosa are not characteristic but may simulat those seen in osteosclerosis due to blood disorders such as leukemia nonleukemic myelosis a d osteoscleroti anemia. The predom nantly sclerotic lesions must be differentiated from those of Paget s disease in which wide cystlike areas of rarefaction are separated by irregular areas of condensation. In urticaria pigmentosa the areas of rarefaction and osteosclerosis are intermingled. In Paget s disease the long bones may be deformed and the skull thickened, but the ribs are rarely involved. It is con cluded that both the cutaneous and bon lesions n urticaria pigmentosa are caused by tissue mast cells.

Release of Histamine in Urticaria Pigmentosa. Bengt H mrin (Lund Un v) reports a case in which acetylsali cylic acid apparently acted as a histamine liberator

Young woman had typical cutaneous lesions of urticaria pigmentosa. X-ray examination of the skeleton showed definit sclerosis, especially in the vertebrae and pelvis. She believed that she wa sensitive to acetylsalicylic acid and olunteered to take test dose of the drug Pronounced circulatory shock resulted from oral administration of 0.25 Gm Several findings during this reaction indicated the symptoms may have been caused by liberation of histamine. These included pronounced drop in blood pressure, high pulse rate, flushed face vomiting of enormous amounts of strongly acid gastric contents and demonstrations of continuous histaminuria.

Acetylsalicyli acid is not commonly recognized as a histamine liberator but the circumstances in th s case were peculia Th amount of histamine stored in the patient s body may ha e been large because the osteosclerotic process is ob iously linked with th presence of mast cells.

▶ [There are many mechanisms by hich drug may cause undesirable systemic effects. If in this case the shocklike reaction was due to liberation of substances from the mast cells, the role of hyaluronidase and heparin, and perhaps even of serotonin, would have to be considered, in addition to histamine.—Eds.]

Solitary Mastocytoma and Mastocytoses Discussion of Mastocytoses and Report of Two Cases of Solitary Mastocytoma Showing Unusual Phenomenon of Generalized Flushing A cording to James Marshall Jean Walker H I Lurie I D L Hansen and David M ckenzie,[4] solitary mastocy

[3] Lancet 1:647 [illegible], Apr 13 1957
[4] South African M J 1:[illegible]-474, Aug. 31, 1957

little attention has been directed to its potential for widespread proliferation This apparently is the first report of tissue mast cells in the peripheral blood of a child they have been reported in an adult. The prolonged bleeding time and tendency to oozing with venipuncture suggest hemorrhagic diathesis that could possibly be related to the potentially high content of heparin in the tissues. The marked disturbance of prothrombin time, with normal clotting time may possibly have been due to profound liver disturbance by infiltration with tissue mast cells and hemorrhage

The striking finding at autopsy was the fluid character of the blood in the peritoneal cavity Thus local hemorrhage within an organ or cavity may be fatal Treatment must be directed primarily at replacement and maintenance of blood volume as well as to correction of associated coagulation defects if possible.

► [The cutaneous lesions in this child, as far as can be determined from the description in the original article, were not the brownish macular lesions usually seen in urticaria pigmentosa. It should be stressed that the mast cells found in the circulating blood were tissue mast cells (round or oval nucleus, rarely indented, with granules varying from fine to coarse) and not blood basophils (small cell body with polymorphous or lobulated nucleus and irregularly distributed granules) —Eds.]

Generalized Osteosclerosis in Urticaria Pigmentosa Radiologic Aspect is described by S Schorr F Sagher and E. Liban[2] (Jerusalem) Progressive bone changes seen in 2 patients during 5 and 2 years respectively indicated that the skeletal lesions like those of the skin are due to tissue mast cell accumulations.

CASE 1 —Man 53 had had a diffuse eruption of the lower trunk and extremities for 4 years. The lesions were brownish, red, macular and showed urtication on stroking Biopsy showed accumulations of mast cells in the midcutis. Chest x rays showed cystic osteoporosis of the ribs with thickening of the bony trabeculae. The skull tables were stippled and thickened. Mild sclerosis was seen in the pelvis and lumbar vertebrae Five years later sclerotic changes in the pelvis had advanced, along with demineralization and islets of condensation in the skull.

CASE 2.—Woman, 55 had a skin eruption diagnosed a urticaria pigmentosa for 5 years. X rays in July 1953 showed sclerosed trabeculae along the ribs, vertebral bodies and skull In March 1955, there was increased trabecular thickening in the ribs and marked sclerosis of the whole bony structure of the vertebrae and pelvis. Both outer and inner skull tables formed one continuous undifferentiated sclerotic density Cortisone therapy combined with nitrogen mustard failed to halt the disease and the patient died in July 1955 Autopsy revealed

(2) Acta radiol 44 575 584, October 1956

ma tocytoses (urtication local erythema, bulla formation, dermographism) must be ascribed to spontaneous or induced release of asoactive substances from mast cell granules. It ha not been proved, however that histamine alone is in ol ed in producing all or any of them There is striking sim ilarity between attacks of the general flushing occasionally noted in mastocytosis and that in metastasizing argentaf finoma. The common factor may be 5-hydroxytryptamine (5HT serotonin enteramine) which occurs in mast and argentaffin cells. It may be purely coi cidental that perma nent t langiectasia and diarrhea, common symptoms of metastasizing argentaffinoma are fou d sometimes with mastocytosis.

Another unsol ed problem s the relation of the fairly common benign mastocytoses to the malignant or poten tially malignant mastocytoses. The mal gnant type shows kin changes quit disti ct from the benign type but seems t be ccompanied at times by the same clinical manifesta tions of isceral involvement. In malignant mastocytosis, the skin is ivory colored, thickened and infiltrated and may be smooth or sown with tiny granular papules. In minor forms, thickening is min mal and color changes and exaggeration of the kin furrow may be visible only at the great folds of the groins nd xillae and may resemble pseud xanthoma elasticum In majo forms, the skin is pachydermatous, but ts consistency is soft as opposed to the hardening felt in l chenification Nodules mall tumors bullae, excoriations and ulcerations may be noted. Pruritus is intense and often accompanied by dermographism. The histologic picture is sim lar t that f the benign forms.

► [As suggested by the authors, it is probably serotonin, released from the mast cells, hich caused the manifestations identical with those of metastasizing carcinoids However as pointed out in the article by West and Parratt in this YEAR BOOK, the situation as to the serotonin content of mast cell in different locations and in different species of animals is highly complicated —Eds]

Pseudoatrophoderma Colli, Acanthosis Nigricans and Confluent and Reticular Papillomatosis. According to Bea trice Maber Kesten (Columbia Univ Presbyterian Med. Center) and Harriet D James[1] (Lahey Clin c) records of patients with these three pigmentary disturbances show that in most instances each *dermatosis retain it* characteristic pattern. Conf ion arises when new terminology is intro-

[1] A.M.A. Arch. Dermat. 75 325-342, April, 1957

toma in man is rare or perhaps rarely recognized. The clinical appearance is remarkably constant The lesion is present at birth or appears soon afterward as a pink red or yellow papule or small plaque on any part of the skin but with predilection for the extremities especially the wrist. For a few weeks or months the lesion may increase in size until it reaches the final state as a round or oval well-circumscribed, reddish to-light brown slightly elevated plaque 1 5 cm in diameter (Fig 23) The rounded surface may be smooth or have an orange skin appearance and a rubbery infiltration is palpable At intervals of several weeks the tumor spontaneously or after irritation suddenly swells becomes red and

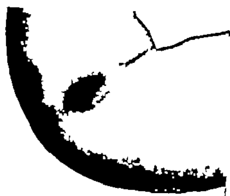


Fig 23.—Solitary mastocytoma on left elbow (Courtesy of Marshall, J et al South African M J 31 867-876 Aug 31 1957)

may have superficial vesicles on its surface. Dermographism of the unaffected skin is demonstrable in some cases. Diagnosis ultimately rests on showing a mast cell infiltrate in the dermis. Many solitary mastocytomas are probably dismissed as moles or banal nevi which in their quiescent state they closely resemble

The flushing phenomenon was noted only once before in a patient with solitary mastocytoma Similar episodes have rarely been reported as occurring in urticaria pigmentosa.

Visceral lesions may be observed with any cutaneous variety of mastocytosis except possibly in solitary mastocytoma in which positive proof of visceral lesions still is lacking Presence of visceral lesions in no way alters prognosis for the worse

The transitory cutaneous phenomena that characterize

atrophoderma colli may be the incomplete form of confluent and reticular papillomatosis. Furthermore so-called pseudo-acanthosis nigricans loses its identity when obesity is interpreted as an associated symptom rather than the cause of confluent and reticular papillomatosis or acanthosis nigricans of the juvenile type

Relation of Juvenile Benign Acanthosis Nigricans to Congenital Malformations was observed by G Marañon and M Alvarez Cascos[4] (Madrid) in 3 patients.

CASE 1.—Boy 11, at birth had manifestations of acanthos nigricans in the xillae and popliteal fossae which also existed in hi mother and brother. Associated conditions were diabetes insipidus, infantilism with arachnodactylia and multiple pigmented nevi. The 17 ketosteroid excretion was 3 1 mg After treatment with thyroxin, Progynon vineydol, itamin A and C, and Pituitrin the infantilism and diabetes insipidus improved, but the acanthosis nigricans was unchanged.

CASE 2.—Boy 11 showed typical manifestations of acanthosi nigricans in the axillae (chiefly in the right) navel and groins, associated with congenital spastic paraplegia (also present in ister) with locomotor disturbances and increased reflexes. After treatment ith thyroidin, the acanthosis nigricans disappeared from both axillae and the na el and groins showed improvement.

CASE 3.—Boy 8, whose parents were first cousins and whose grandmother had diabetes, showed acanthosis nigricans in the corners of the mouth on the neck, axillae, antecubital fossae and navel since birth, along with other abnormalities, including macrosomia, marble disease of the bones, li er cirrhosis with hyperlipemia, patent ductus arteriosus and ocular malformations, such as bilateral myopic astigmatism, myelin fibers in the retina laterally from the right optic nerve and minor bilateral opacities f the itreous body The 17-ketosteroid excretion was 3.72 mg

The acanthosis nigrican was associated with other congenital malformations e g arachnodactyl infantilism and ne in Case 1 hereditary spasti paraplegia in Case 2, and patent d ctus arteriosus, ocular malformations and fatty liver cirrhosis in Case 3 In 2 patients, the acanthosis nigricans w s accompanied by endocrine disturbances (diabetes ins pidu in Case 1 and macrosomia probably due to hyperpitu tarism in Case 3) In both, 17-ketosteroid excretion was decreased (d enal insufficiency?) Association of juvenile be ign acanthos gricans and congenital malformatio suggests a genodermatosis

Lethal Congenital Bullous Ichthyosiform Erythroderma. S Lapière (Liège, Belgium) reports an excellent exam

(7) Acta dermat venereol. 37 244 258, 1
Ann dermat et syph 84 1-21, Jan Feb, 1957

duced that covers some of these disorders together with somewhat similar papillary dystrophies Confusion also arises when patients have lesions characteristic of two of the diseases

Pigmented papillary dystrophies resembling acanthosis nigricans have been reported in obese and nonobese women with darkly pigmented skin In patients with lesions of this type those of acanthosis nigricans and those of confluent and reticular papillomatosis diagnosis of pseudoacanthosis nigricans has been made.

In 5 Negro patients with confluent and reticular papillomatosis observed by the authors the topography characteristic confluent and reticular pattern and atrophic lesions did not suggest the clinical diagnosis of acantho is nigrican However sections from the confluent pigmented papillary lesion of the intermammary region in 1 patient were indistinguishable from those of a Negro boy with acanthosis nigricans

To add to the confusion the 5 patients had besides the confluent pigmented pattern in the midline of the torso, what appeared to be pseudoatrophoderma colli From descriptions and photographs of patients with pseudoatrophoderma colli and observations on these 5 patients the possibility is suggested that pseudoatrophoderma colli is a form of confluent and reticular papillomatosis The lesions in confluent and reticular papillomatosis are initially minute papules in the intermammary region which fuse to form flat hyperpigmented areas whereas pseudoatrophoderma colli begins as mottled pigmentation on the neck As the lesions of each spread over the thorax and neck in reticulated or mottled pattern with atrophic or pseudoatrophic lesions in the gaps they seem indistinguishable

In histologic studies of the various types of lesions in the 5 patients, the depigmented atrophic areas showed changes similar to those described in pseudoatrophoderma colli and the hyperpigmented furrowed and at times papillary areas showed changes observed in confluent and reticular papillomatosis or acanthosis nigricans

From the clinical and histologic study of these patient it appears that in confluent and reticular papillomatosi all lesions characteristic of pseudoatrophoderma colli may occur Analogous to the forme fruste of neurofibromatosis p eudo-

Skin peeled off with great ease Simple obstetric maneuvers had denuded the arms, legs neck and posterior lumbar region (Fig 24) The 2d day despite soft swaddling in amidon glycerol there was increased dropping off of the horny layer exposing the prickle cell layer except on the back and occiput Desquamation increased continually but the ulcers remained superficial and some tended toward epidermization I tense purpura developed the 4th day especially in the de n ded areas and the patient died in cardiovascular collapse Autopsy showed hemorrhagic men ngitis and pulmonary edema. Histologic skin changes were typical of erythroderma with extensive bullous desquamation (table)

Lapière fa ors subclassification of Brocq s congenital ich thyosiform erythroderma into two types (table) ordinary or nonbullous, and bullous, both appearing in severe, lethal form and also in benign form compatible with l fe Nonbul lous congen tal ichthyosiform erythrodermas are more nu merous and better known. The most serious cases present as harlequin fetuses, dead at birth or within a few hours and correspond to type I of Riecke classification. Those that survive constitute Riecke s types II and III Aside from the present case, only one description by Bizard and Langeron (1908) of bullous congenital ichthyosiform erythroderma is known t exist n the l terature

CONGENITAL ICHTHYOSIFORM ERYTHRODERMAS

NONBULLOUS ICHTHYOSIFORM ERYTHRODERMA	BULLOUS ICHTHYOSIFORM CONGENITAL ERYTHRODERMA
Anatomopathologic Examination	
Basal layer well formed prickle cell layers thick with normal cells furnished ith a normal fibrillary net ork passing from one cell to the other Granular layer contains abundant keratohyaline granules Str tum lucidum well delineated horny layer compact and solid, homogeneous without parakera tosis.	Basal layer well formed thick prickle cell layers. From the sec ond or third layer there is a dis integration of fibrils, cavitary atrophy of all the protoplasm with perinuclear vacuoles nuclei them selves degenerated intercellular membranes thickened without acantholysis with persistence of Bizzozero nodules. N spongio sis or distended Cells. Finally, there is reticular formation of the superficial prickle layers and in the entire granular layer Bullae form in this fragile reticu lated layer by tearing. Horny layer is not very compact, ith lamellae separated from each other revealing remains of nuclei and nucleoli.

ple of this rare hereditary disease. The family history of a female infant, who lived only 4 days, was as follows The grandmother had congenital bullous ichthyosiform erythroderma (Riecke type II) the only one of numerous siblings so affected At birth she had been covered with erythrodermic bullae and ulcers without perceptible hyperkeratosis, but this appeared at age 3 or 4 when the bullous lesions diminished. Of her 6 children 1 was born with large bullae and epidermal desquamation and lived only a few weeks.



Fig 24 —Cutaneous covering is erythrodermic throughout Superficial portions of epidermis peel off easily (Nikolsky sign) Mucous surface is denuded. Epidermis not hyperkeratotic except on palms and soles. (Courtesy of Laplère, S. Ann dermat. et syph 84 5-21 Jan. Feb., 1957)

Another born with the same symptoms survived to become the mother of the present patient

This young mother had continued to have bullous skin lesions intermittently but displayed hyperkeratosis similar to her mother s which was not disfiguring She married young and lost her first child male within a few hours after he was born covered with bullae and ulcers. The second child was normal. The third also male was born with the same skin affliction as the first and lived 4 days The present female infant was the fourth child

At birth her entire skin appeared erythematous it was supple but in some places slightly rough The whitish palms and soles seemed thick the lids and mucosae were normal.

Hyperkeratosis palmoplantaris with periodontosis is inherited as a recessive. Parental consanguinity has been noted at least 4 times. Both sexes are affected. The authors believe that this anomaly should be distinguished from Meleda's disease and keratoma palmoplantaris (Unna Thost).

Diagnosis of Meleda's disease (hyperkeratosis palmoplantaris hereditaria progrediens) should be restricted to patients showing (1) eccentric glovelike expansion of hyperkera-

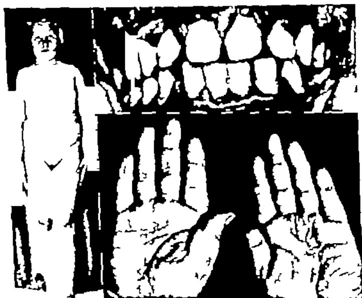


Fig. 25 (left).—Girl, 10, with hyperkeratosis palmoplantaris (Papillon Lefèvre).
Fig. 26 (above right).—Periodontosis.
Fig. 27 (below right).—Palmar changes.
(Courtesy of Jansen, L. H. and Dekker, G.: Dermatologica 113:207-219, October, 1956.)

tosis palmoplantaris, often involving the elbows and knees, (2) marked hyperkeratosis usually with deep fissures, (3) transmission as a recessive and (4) no dental anomalies.

Keratoma palmoplantaris (Unna Thost) is characterized by (1) severe hyperkeratosis restricted to the palms and soles and appearing early in life, (2) absence of dental anomalies and (3) dominant inheritance.

The authors report on a girl, aged 10, with hyperkeratosis palmoplantaris and periodontosis (Figs. 25 and 26). Skin

Congenital Ichthyosiform Erythrodermas (Cont)

Nonbullous Ichthyosiform Erythroderma	Bullous Ichthyosiform Congenital Erythroderma
Severe Lethal Types	
Severe lethal type is the harlequin fetus or congenital diffuse malignant keratoma.	Malignant lethal type, as described above an erythroderma with vast bullous desquamations. There is no hyperkeratosis.
Benign Types	
Benign types present generalized hyperkeratosis of hystrix type, often erythrodermic, more marked in skin folds keratosis is solid and adherent. There are no bullous lesions	Benign types present less generalized hyperkeratosis face is less involved. Other regions are spared folds are most affected with hyperkeratosis of palms and soles erythroderma is regularly present keratosis is more porous, lamellar and easily detachable. Disease commences from birth with purely bullous attacks superimposed on erythroderma. Bullous process progressively gives way to hyperkeratosis which appears at age 5-10. Sometimes bullous process is no longer clinically perceptible, but histologic study discloses reticular degeneration which constitutes potential bullae.
Localized Types	
Certain palmar plantar hyperkeratoses belong in this group	Certain palmar plantar hyperkeratoses with episodic bullae show the characteristic reticulated formation histologically

Hyperkeratosis Palmoplantaris with Periodontosis (Papillon Lefèvre) is reported by L. H Jansen and G Dekker[1] (Univ of Utrecht) In all cases the palms show a sharply limited hyperkeratosis The skin is red and parchment-like with accentuation of normal markings The hyperkeratosis is seldom severe enough to cause serious discomfort Some scaling is present especially at the edges of the palms. The soles show a similar eruption which may extend to the Achilles region and the external malleoli Scaly red patches may occur over the anterior tibial surfaces and dorsa of the fingers and toes Nails and hair are normal and hyperhidrosis of the hands and feet is present The skin changes usually appear during the first 3 years of life

After deciduous teeth appear periodontosis develops at age 2 or 3 Dystrophy of processus alveolaris combined with inflammation of gums results in loss of teeth Inflammation then subsides but reappears after eruption of permanent teeth.

(1) Dermatologica 113:207 219 October 1 56.

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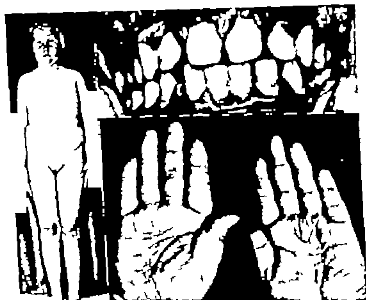


Fig 25 (left) —Girl, 10, with hyperkeratosis palmoplantaris (Papillon-Lefèvre)
Fig 26 (above right) —Periodontosis.
Fig 27 (below right) —Palms [illegible].
(Courtesy of James, L H and Dekker G Dermatologica 11:207 21 October 1954)

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changes had appeared at age 1½ and consisted of sharply defined hyperkeratosis with redness thickening slight scaling and superficial fissuring of the palms (Fig 27) and soles. The gums (Fig 26) showed marked glossy marginal tumefaction soft consistency and easy bleeding Deep pockets containing pus were present.

► [A very rare form of palmar and plantar hyperkeratosis which, as shown in Figures 25 27 clinically appears quite different from Meleda disease.

In the original article the authors suggest investigation of cases of periodontosis in dental clinics for associated palmar and plantar skin changes. In this manner a more accurate estimate as to the number of persons showing this syndrome might be obtained.—Eds.]

Familial Granuloma Annulare Report of Two Cases, with Observations on Incidence of the Disease in Britain. Arthur Rook Royden Davis and Danilo Stevanovic[9] (Cambridge, England) observed a brother and sister aged 14 and 12, with granuloma annulare Lesions appeared first on the boy and within 1 or 2 weeks on the girl Granuloma annulare is common enough that occurrence of more than one case in a family could be attributed purely to chance However the more or less simultaneous development of the lesions in these children and in other familial cases reported in the literature may have greater significance The rarity of these lesions in familial cases is their most interesting feature If the hypothesis were correct that granuloma annulare is a special reaction to miscellaneous infective or toxic agents, dependent on some unknown constitutional factor familial cases might be expected to occur more often The same objection applies to attempts to incriminate a specific infective agent

One of the authors observed 50 cases of granuloma annulare among about 21 000 cases of skin disease—an incidence of 0.24% In this group 56% of the patients were in their 3d and 4th decades and only 16% were aged 10 or under These figures suggest that incidence may be increasing in Britain and that it may be affecting an older age group than formerly was the case.

Erythema Annulare Centrifugum (Darier) in Newborn Infant is reported by Ralph Fried Irving L. Schonberg and Jerome Z Litt[1] (Mount Sinai Hosp Cleveland) This case is distinctive in that it occurred within 24 hours of birth a circumstance not reported previously

(9) Acta dermat.-venereol 37 160 164, 1957
(1) J Pediat. 50 66 67 January 1957

In newborn boy hives developed shortly after birth, but soon began to clear centrally. The borders grew centrifugally, were indurated, red, raised and had a rubbery feel. The borders soon broke up and assumed gyrate, scalloped and arciform arrangements over the entire body with the exception of the palms and soles. There was little scaling. After the first injection of diphtheria-whooping cough-tetanus toxoid, the lesions disappeared completely for 48 hours, but they promptly recurred. There was no change after administration of the booster dose about a month later. New lesions continued to develop and progress without cessation. There was no noteworthy family history or prenatal disease. The mother took aspirin, phenacetin and codeine approximately every 2 weeks for recurrent backaches. The etiologic factor has yet to be determined.

► [A remarkable case. In the absence of other etiologic factors, the aspirin, phenacetin and codeine must be suspect, although it would be unlikely that the eruption would last as long as it did (7 months at the time of report) if any one of these drugs were responsible.—Eds.]

Cytologic Studies in Lichen Ruber Planus. Nils Thyresson and Gunnar Moberger[2] studied material from 25 cases and found that the pathologic lesion in lichen planus appears to start intraepidermally. As a reaction to the epithelial lesion leukocytes escape around the superficial blood vessels in the corium to wander in toward the epithelial lesion. Colloid bodies (Fig. 28) occur early in the epithelium, where it is possible to follow individual epithelial cells during development into a completely colloidally transformed cell with a laterally displaced pyknotic nucleus. The primary focus develops into a micro-abscess. In increasing abundance, leukocytes stream in from underlying papillae and in the corium an inflammatory reaction of nonspecific character develops. The epithelium connective tissue margin disintegrates and a distinct pinching off of colloidally transformed epithelial cells can be observed in the inflammatory infiltrate. In a later stage accumulations of colloidally transformed cells with or without a retained pyknotic nucleus appear in the corium. This last change is the one commonly observed. In the late stage more or less abundant cell infiltrate is found in the corium and only occasional colloid bodies can be seen.

Absorption analysis in ultraviolet proves that the substance appearing in stained preparations as colloidal is characterized by high absorption at 257 mμ and, accordingly contains nucleoproteins in high concentration. The substance does not give a positive Feulgen reaction; thus the nucleic acids in these nucleoproteins seem to be of ribose type.

(2) Acta dermat.-venereol. 37: 91, 1957.

Free and protein bound sulfhydryl groups are essential to such vital cell functions as cell growth and division. The occurrence of such groups in high concentration is an expression of vital cell function. In a modification of the Barrnett Seligman histochemical SH reaction the "colloid substance" appears with greater intensity of stain than the surrounding epithelial cells and thus contains an increased quantity of reactive sulfhydryl groups.

The changes undergone by the epithelial cells in lichen ruber planus show strong and striking resemblance to the



Fig. 28 — Intraepithelial shrunken "colloid" bod[y] cell with partly vacuolized cytoplasm and considerably enlarged nucleolus; reduced from ×1400. (Courtesy of Thyresson, N., and Moberger, G.: Acta dermat venereol 37:191-204, 1957.)

course in molluscum contagiosum caused by a known high-molecular virus. Cell changes of this type do not occur in other known pathologic conditions in the epithelium of the skin except in those caused by virus infections (with the exception of certain carcinomas originating from the stratified squamous epithelium). The opinion prevailing in the literature that the actual cell changes are of solely degenerative nature is not consistent with the increased quantity of active sulfhydryl groups demonstrable in the colloidally transformed cells.

The authors feel that the cytomorphologic and cytochemical changes observed strongly support the contention that the colloid transformation in early stages of lichen ruber planus is due to an intracellularly vegetating low molecular

virus. The inflammatory changes characteristic of the disease are secondary to this infection.

Histopathogenesis of Lichen Ruber Planus. Many signs and symptoms point at systemic involvement in a predominantly dermatotropic infection in lichen ruber planus. V Aplas[3] (Univ of Erlangen) attempts to support this hypothesis by histopathogenic findings. Since Kobner it has been known that the initial changes in lichen ruber planus consist of vasodilatation and perivascular infiltration. The character of these infiltration cells, i.e. whether they emigrate from the blood stream or proliferate in loco is still under discussion.

The author feels that the initial exudative process is soon followed by a rapid growth of perivascular lymphoid pluripotent mesenchymal cells and that the intensive pericapillary proliferation of these reticulohistiocytic elements displaces and even destroys the original connective tissue and capillaries. This explains why capillaries are so scanty at the top of a lichen ruber planus papule. Larger vessels also show marked alterations e.g. swelling of endothelial elements, obliteration of vascular lumens and hyalinization of vascular walls. With progressing cell proliferation, eventually a small nodular granuloma like structure forms, which does not correspond to the prototype of infectious granuloma (tuberculous granuloma) but has in common with the latter that all cells derive from perivascular and/or subendothelial undifferentiated mesenchymal cellular elements. Assuming that the proliferating cells in lichen ruber planus originate from these subendothelial and/or pericapillary undifferentiated mesenchymal cells and, therefore belong to the reticulohistiocytic system they must then display the characteristics of the latter namely phagocytosis, intracellular digestion and formation of reticula fibrils (gitterfasern) all of which could be seen in histologic sections and by cytologic examination.

Among the so-called infiltrating cells larger elements were found with abundant dull blue cytoplasm, one or several dendritic processes, vacuoles, nuclear detritus, and round or slightly indented nucleus with a pale, granular filamentous chromatin stroma, which are characteristics of functioning histiocytes. In Giemsa-stained smears, these cells show sin-

(3) Arch. klin. exper. Dermat. 204 297 308, 1957

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o allergic response of the vessel wall (Schoenlein Henoch purpura and chronic allergic purpura) (6) purpura due to qualitatn e and quantitative platelet deficiency (7) purpura d e to deficiency of blood coagulation mechanism and (8) purpura due to dy protemenmas.

Occasionally patients with gravitational purpura have generalized purpuric lesions and cap llary fragility Appar ently the persistent capillary damage in one part of the body may prod ce changes in the capillaries in other parts by a mechanism similar to the autosensitization eruption of eczema.

Schoenlein Henoch purpura can, in a typical case be distinguished from other forms of purpura on clinical grounds, but it may be difficult to differentiate from acute rheumatism and occasionally periarteritis nodosa. The name purpura is eally a misnomer as the in tial skin lesion is an urticarial papule It becomes dusky red and a central purpuric spot ma ppear As the eruption fades a faint brown tinge is left. Only the lesions on the legs may be frankly purpuric but occasionally small petechiae and ecchymosis form distinct from the urticarial exanthem. A Koebner phenomenon can be demonstrated in the erupti e phase, although increased capillary fragility is rarely f und.

Purpura due to drugs may be caused by (1) damage to platelet formation in the bone marrow producing true thrombocytopenic purpura (2) production of a circulati g anti body which, in the presence of the drug and complement, lyses the platelets and damages the capillaries and (3) true vascular damage without evidence of effect on blood element

In diabetes and hyperten ion purpura may occur as the result of ascular damage Examination of the nail bed capillaries may show tortuous and irregular loops, which are of alue in confirming general capillary disease.

The author suggests that endothelium may possibly be sensitized like epidermis and that such sensitization may oc cu from endogenous and exogenous allergens.

Schönlein-Henoch Syndrome with Particular Reference to Renal Sequelae. R. J Derham and M M Rogerson[8] (Liver pool) in est gated incidence of renal sequelae in 94 patients with Schönlein-Henoch yndrome 35 of whom were pre-

[8] Arch Dis Childhood 31 344 348 October 956.

gle or conglomerate bluish red granules, i e signs of intracellular digestion By silver impregnation (Gomori) gitter fasern could be demonstrated which under the electron microscope consisted of bundles of thin nonbranching striated protofibrils The latter show transition into collagen fibrils (precollagen fibrils) In silver impregnated section silver is deposited in the inner parts of collagen fibrils but on the surface of reticular fibrils.

It is concluded that the infiltrate cells of lichen ruber planus are proliferating elements of the reticulohistiocytic cellular apparatus of the smallest cutaneous vessels. The pluripotent undifferentiated mesenchymal cells in the perivascular zones make the formation of morphologically and functionally different cells possible, and their capacity to form reticular fibrils can be shown by silver impregnation The apparently dermatotropic infectious virus of lichen ruber planus affects not only the cellular apparatus of the smallest cutaneous vessels but also causes primary alterations of the epidermis, responding to the virus with cellular proliferation and degeneration

Purpura as Seen by the Dermatologist. I B Sneddon[4] (Sheffield England) states that the most important factor in all forms of purpura is the capillary wall As long as this remains undamaged platelets can be removed experimentally from the blood without purpura occurring and the blood may be made incoagulable with heparin or Dicumarol® without resultant purpura After excluding all purpuric eruptions with hematologic abnormalities there remain several types in which the cause is primarily an increase in permeability or fragility of the capillary wall Most dermatologic purpura cases fall into this group of vascular purpuras.

Based on the presumptive pathogenic mechanism the following classification is suggested (1) congenital defects of capillary wall (Ehlers Danlos syndrome) (2) increased vascular permeability (scurvy) (3) increased vascular fragility (purpura simplex senile purpura mechanical and orthostatic purpura purpura of diabetes hypertension and uremia, vascular purpura due to drugs textile purpura and Loewenthal s itching purpura) (4) chronic vascular purpura (Schamberg s disease Majocchi s disease and pigmented purpuric eruption of Gougerot) (5) syndromes due

(4) Acta derm venereol. 37 294-305 1957

A. Larcan[a] (Metz France) observed 10 (3.3%) with various types of cutaneous lesions. In 8 the lesions were primary and in 3 they represented the first signs of the rheumatic affection and had diagnostic value. In 6, there were transitory cardiac signs which had completely disappeared on discharge. Several were re-examined at different times and they remained free from cardiopathy

In all patients despite the intensity of cutaneous manifestations (especially n 3) there was no evidence of severe visceral organic involvement, and the usual treatment with salicylates, Butazolidin® or cortical hormones brought prompt relief and cure after 3 weeks to a month.

Two patients exhibited the specific skin lesions of rheumatic disease—Besnier s discoid erythema and Lehndorff Leiner s erythema annulare. These are dark, copper-colored spots nonpruriginous with a clear center 3-4 mm in diameter slightly elevated and with a definite border sometimes polycyclic or annular The sites of predilection are the thorax, flank and lumbar region the face and flexure folds are spared. They are transitory migrant and recurrent, usually lasting not over 72 hours.

Other dermal lesions seen in patients with rheumatic disease include maculopapular or papular erythema and erythemas f morbill form, scarlatin form and polymorphous types. Purpura, though generally rare, was observed in 4

Although numerous authorities regard the presence of cutaneous lesions s a serious prognosti sign, indicating a severe heumatic ndocard tis this was not true of the 10 adults tud ed. Th authors believe that the reported severity of cutaneous types of rheumatic disease in children is attributable to its greater se erity in young patients and that published data emanate from pediatric hospitals, where the most severe cases re seen.

Some Observations on Hyperglobulinemic Purpura (Waldenstrom s Syndrome) in 3 patients are presented by Wi liam F Symon (Bluffton, Ind) Robert J Rohn and Wil liam H Bond (Indiana Uni) The syndrome has been observed most often n middle-aged women, but men are not excluded. The promi ent, con istent finding is that of episodic howers of petechiae which may occur on all parts of

Presse méd 64 1970 1972, Nov 24, 1956
77) Am J M Sc 234 160-69 August, 1957

viously reported During initial illness 46 of the 94 children had some renal involvement. Of the 59 patients in the present series (1951 55) 2 died A girl aged 11 died of cardiac failure and chronic nephritis 10 weeks after admission. She had 5 recurrences of the rash and repeated attacks of colic and hematuria during her illness. The other patient, a boy aged 6 died in uremia 11 weeks after admission. On admission, he had purpura, abdominal colic and joint swellings but did not have renal complications until 2 weeks later when albuminuria hematuria anuria and hypertension occurred. Typical purpuric rash was present in all. Among 19 patients, however before the rash appeared joint swelling occurred in 10 and 9 had abdominal pain. In 1 patient the rash was so severe that necrosis occurred.

Albumin and red cells were still present in the urine of 13 of the 94 patients when they left the hospital. Follow up with Addis counts and urea clearance tests showed that 9 of the 13 patients no longer had evidence of kidney disease whereas 4 had chronic nephritis Two children in whom kidney function became normal had had albuminuria and recurrent hematuria for more than 7 years Five children without renal involvement at the time of the original illness and who remained symptom free had some impairment of renal function, as shown by Addis counts and urea clearance tests.

There is general agreement that the greatest danger of the Schonlein Henoch syndrome is renal damage Such damage is indicated by albuminuria hematuria or both but it has not been established that these findings constitute acute glomerulonephritis Neither facial edema nor hypertension are commonly noted nitrogen retention is rare and the erythrocyte sedimentation rate tends to return to normal despite continued hematuria More leukocytes are present in the urine than in most cases of acute nephritis This atypical picture might be described as renal bleeding yet such early involvement often is followed by lasting renal damage

Recurrences of the syndrome especially with renal symptoms, have been considered detrimental to the ultimate prognosis, but this assumption did not always prove correct in the present series. Two patients with several recurrences eventually showed normal renal function

Erythema and Purpura in Course of Rheumatic Disease in Adults. Among 300 young adult (18-42) C Ablard and

The second patient had a generalized infected eruption that appeared first on the buttocks. The third had seborrheic dermatitis of the scalp, an eczematoid dermatitis about the ears and a generalized maculopapular eruption. The fourth had recurrent attacks of a maculopapular eruption resembling heat rash, and the fifth had severe seborrhea of the scalp and severe dry eczema over the entire body

In 4 of the 5 children milk allergy was strongly suspected as a major factor in producing the eczema 3 had positive skin tests to milk or other foods. Three children had a family history of eczema and in 4 eosinophilia was found (14-45%)

Four patients had splenectomy all showed temporary hematologic improvement, but 3 quickly relapsed clinically and hematologically After splenectomy fulminating infections developed in all 4 Two of the children had meningitis 3 and 8 months after operation. One died suddenly of pneumonia and septicemia 2 months after surgery and 1 died of basilar meningitis 3 weeks after operation. Four lived about years 1 survived to age 7½ Three of the children had family histories compatible with transmission of their disease as a sex-linked recessive trait. Two were brothers and one ther brother not included in this group had been similarly affected. The hereditary pattern and the combination of symptoms differentiat these patients from most children with eczema or purpura.

► [The thrombocytopenic purpura, purulent otitis media and fulminating infections after splenectomy were present uniformly in these patients. However the cutaneous manifestations, as far as can be judged from the descriptions in this paper ere not uniform, and it is not possible to tell whether they belong in the category of eczema and, if so, which particular form.—*Eds*]

A Family Reunion Study of Hereditary Hemorrhagic Telangiectasia in a large family s presented by Robert M Bird James F Hammarsten, Richard A. Marshall and R R Robinson* (Univ of Oklahoma) with the technical assistance f Esther Beckner Of 170 blood relatives 32 (19%) were ffected. The mode of geneti transmission was that of a simpl mend lian autosomal dominant. There was no sex predilection If parent survived to age 30, no generations were skipped. Genetic linkage between hereditary hemorrhagic telangiectasia nd certain blood groups was sought but not found.

The haracteristic early lesion is disti ctly different from

* New England J Med 257 181-184 July 18 1957

the body but are most numerous on the lower extremities. The bleeding tendency is limited to the skin in most instances It apparently is due to an abnormality of the capillary wall as evidenced by a positive Rumpel Leede phenomenon and absence of clearcut coagulation mechanism defect. A sensation of dryness of the eyes and mouth are common. Generalized lymphadenopathy is usual, and moderate enlargement of the liver and spleen may occur The syndrome tends to run a chronic, benign course although in 1 patient there was an associated disseminated reticulum cell sarcoma

There usually is normocytic normochromic anemia of moderate degree and accelerated erythrocyte sedimentation rate Slight to moderate autoagglutination of erythrocytes often is present The serum albumin usually is slightly decreased and the serum globulin relatively and absolutely increased. Electrophoretic analysis of the serum places the increased globulin protein in the gamma fraction Most often the gamma peak is rounded suggesting heterogeneous composition No cryoglobulins were detected

Hyperglobulinemic purpura represents a peculiar response possibly allergic, of an irritated reticuloendothelial system that may or may not accompany a definite disease process. The association of increase in gamma globulin with capillary fragility has yet to be explained

► [Many forms of treatment, including adequate doses of triamcinolone tried in a patient under our observation failed to produce any benefit.—Eds.]

Eczema Associated with Thrombocytopenic Purpura and Purulent Otitis Media Report of Five Fatal Cases is presented by Carolyn C Huntley and Susan C Dees[8] (Duke Univ) All the patients were boys aged 2 month to 6 years Bleeding was the initial symptom in 4 and purulent otitis in 1 Bleeding occurred at age 2 weeks in 3 patients and at 3 months in 1 All 5 patients had otitis media There was no constant ear flora although beta hemolytic streptococci pseudomonas and proteus were present at some time in all cases in which cultures were made The frequency of gram negative organisms may have been due to previous long term antibiotic therapy

Cutaneous eruptions were present at one time or another in all patients. One patient had a maculopapular crusted scalp eruption and the rest of the skin was dry and scaly

(8) Pediatrics 19 351 361 March 19 7

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The haracteristic early lesion is distinctly different from

* New England J Med 257 105-109 July 18, 1957

a *spider angioma* The typical lesion is a macule that resembles a crushed spider 2 3 mm in diameter cherry red and not elevated (Fig 29) In the absence of recent hemorrhage and anemia, great pressure is required to obscure the lesions and definite pulsations are absent The larger nodules and spider like lesions usually appear in the skin later in the disease Overt telangiectases become increasingly manifest with age. The commonest sites of involvement are the face, lips nares tongue ears and hands. Although the telangiectases themselves do not pulsate, hemorrhage from lesions in



Fig 29—Typical lesions of congenital hemorrhagic telangiectasia. (Courtesy of Bird, R. M et al. New England J Med. 257 105-109 July 18, 1957)

the nose or tongue are often profuse and pulsatile as if an artery were severed.

In the present family gastrointestinal or genitourinary bleeding occurred only in those with a history of bleeding from a more accessible site Recurrent nasal hemorrhage occurred in childhood in 85% of patients Seven of 10 persons over 50 had severe hemorrhages from one or more sites whereas in those under 50 all bleeding was mild One member of the family died of hemorrhage

Cirsoid Aneurysm in Skin Case Report is presented by Hans H Biberstein and Max Jessner[1] (New York Univ Post Graduate Med. School and Skin and Cancer Unit)

Man, 54 had a lentil sized, dull brownish red barely raised "tumor present for many years excised from the left zygomatic area. Histologic examination revealed a vascular origin, probably arterial,

(1) Dermatologica 113 129-141 1 56.

and nodular arrangement of the components. Significant features for classification were location in the cutis and composition of blood vessels. The walls of the vessels were massive, consisting of a single layer of endothelium surrounded by circularly arranged, nucleated spindle cells and finally by a thick ring of elastica.

Cirsoid aneurysms may be congenital in origin, arteriosclerotic, syphilitic, embolic, related to periarteritis nodosa, amyloidosis or colloid degeneration of the vascular wall, and, primarily traumatic. In the present case, a congenital anlage and unnoticed trauma were considered possible etiologic factors. Arterial angioma was ruled out because of the absence of vascular neoplastic processes.

Changes in Oral Mucosa in Malignant Intestinal Carcinoidosis re described by H Schuermann and O Hornstein (Univ of Wurzburg)

Woman, 51 undernourished, had had fleeting flushes for several years. They were accompanied by purplish discoloration of the face, lasted each time only for a few minutes and closely simulated drug eruptions. She also complained of "burning on and under the tongue" and of occasional severe burning of the face. On the left border of the tongue, in its anterior half, there was a circumscribed, rough protuberance of the mucosa, about 1 cm. long, consisting of three closely adjacent, lentil-sized nodules. This mass was rather superficial, not tender to touch and covered by an inconspicuous mucosa. The right buccal mucosa contained two yellowish, millet sized nodules, slightly emerging from the mucosal surface. The mucosa of the lower lip showed cheilitis glandularis simplex. The regional lymph nodes were not enlarged.

Histologic studies of the biopsy specimen from the tongue lesion showed nothing particular in the basal and suprabasal layers except increased acanthosis and relatively increase in cellules claires. The tunica propria was widened by circumscribed areas of connective tissue hyperplasia, in the lower half of which there was cellular whirl-formation (predominantly Schwann cells) and plump swelling of small and medium nerve trunks, similar to spindle-shaped neuromas. I the midst of larger nodule, nerve trunk was seen "losing itself" among proliferating cells. Other nerv trunks ppeared inconspicuous

These observations imply that the carcinoid syndrome n- ol es also the kin Thus, fleeti g attacks of erythrocyanosis affect g mainly th upper half of the body and accompanied by burning or itching sensations should suggest ca cinoidosis, especially in the presence of vague abdominal complaint and cardiovascular symptoms often related to the ght heart.

Since the histologic ppearance of the carcinoid in the mall intestine is lso characterized by a proliferation of

nerve tissue it may be assumed that the mucosal changes in the oral cavity represent the histologic manifestations of the same disease in an unusual localization.

Congenital Dyskeratosis (Zinsser Cole-Engman Type) Associated with Constitutional Myelopathy (Thrombopenic and Neutropenic Purpura) A Bazex and A Dupre[3] (Toulouse France) report the eleventh case of this type the first observed in France. Almost simultaneously in 1926, Cole and associates and Engman reported similar cases displaying reticular pigmentation buccal leukoplakia and ungual dystrophy but Zinsser in 1910 had already described the same syndrome Cole s designation of dyskeratosis congenita has prevailed in the later reports 6 of which originated in the United States and 4 in Europe.

Besides the classic triad the authors patient a boy 11 had severe myelopathy (a dissociated medullary aplasia) with thrombopenia and granulopenia which progressed concomitantly with cutaneous lesions. Hemorrhagic purpura, with repeated epistaxis alternating with gingival hemorrhages due to rupture of hemorrhagic mucosal bullae required dozens of blood transfusions. The patient s general condition was poor In this case the dermatosis was completely overshadowed by the serious hemopathy

All 11 cases of congenital dyskeratosis appeared in males. Three occurred in brothers Hereditary transmission appears to be recessive since parents are always normal. Age at onset of cutaneous lesions was 5-12 years.

Aside from poikiloderma buccal leukoplakia and dystrophy of the nails hyperhidrosis of palms and soles appeared in all patients. Other abnormalities included vasomotor disturbances (cyanosis of the extremities and facial erythema) cutaneous bullae pluriorificial lesions e.g., postbullous buccal ulcers perlèche anorectal and urethral lesions ob truction of lacrimal duct bullou conjunctivitis and tympanic lesions also abnormalities of the hair and teeth

Although the present case is unique in its association of an acute malignant hemopathy with congenital dyskeratosis hematologic disturbances particularly splenomegaly have been mentioned by other authors Other general signs reported in congenital dyskeratoses include testicular atrophy

(3) Ann. dermat. et syph. 84 4 7 513 Sept Oct 1957

h poadrenalism dysphagia, cardiac anomalies, osteoporosis hernia and hypospadias.

Two hypotheses are ad anced as to the relation of cuta neous lesions to the myelopathy (1) both are due to a com mon genetic defect or (2) the primary d sturbance i strictly medullary and lesions of skin and mucosa are merely their superficial manifestation, as acanthosis nigricans is an indication of deep cancer and the Plummer Vinson syndrome of anemia.

It seems justifiable to classify congen tal dyskeratosis of Zinsser-Cole Engman into two types the purely mucocu taneous and the type with const tutional myelopathy since prognosi i the two essentially different.

Observations on Etiology of Dwarfism in Congenital Telangiectatic Erythema are presented by D A. H llman J D Crawf rd and N B Talbot (Massachusetts Gen'l Hosp)

Boy 6, as 96 cm tall and weighed 11.25 kg In terms of normal height and weight, height-age was 3 and weight-age 1½ years. Over the malar regions and lower eyelids, an eczematous rash with areas of increased vascularity and hyperkeratosis was present. Small ulcers ere noted on the soft palate, and the lips were cracked and crusted. Areas of depigmentation and café-au-lait spots were present on the trunk The eruption on the face became worse on exposure to sunlight. Externa investigation failed to reveal any recognizable endocrine or organic causes for the dwarfism.

Attempts were made to augment caloric intake by supplemental feedings, but he refused to take additional food. Cortisone was administered, with marked improvement in appetite. Rapid weight gain and slight slowing of linear growth occurred When cortisone was discontinued, appetite diminished and weight loss occurred, but linear growth rate accelerated from 3.1 to 7.6 cm./yea Subsequent administration and withdrawal of cortisone led to repetition of these events. During about 2 years, he grew about 4 cm more than would have been predicted from the pretreatment growth rate (Fig 30)

The lesion in the kin and mucous membranes and hy persen iti ty to sunl ght in this patient were simila to find g reported in congenital telangiectatic erythema in dwarf Hypocaloric dwarfism is a presumptive diagnosis mad when patient is underheight for ge and underweight for height. Diagnos is established by howing that growth rates can be normal or higher than normal when caloric t re ar mproved. The data in the authors case appear to support this diagnosis. The greatest weight gains were noted

Pediatrics 20 268 271, August, 1957

during cortisone therapy but linear growth increases were delayed until cortisone was discontinued. This may have been due to the growth suppressing action of cortisone. Gain in height occurred without the excessive advance in

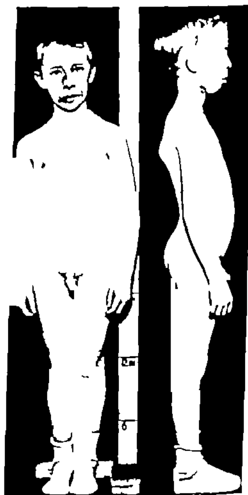


Fig 30.—Patient at 8½ years, with height-age of 4½ and sight-age of 3½. Facial skin shows areas of erythema and atrophy with ulcerations of lips and lower eyelids. (Courtesy of Hillman, D A et al. Pediatrics 20 268-271 August, 1957.)

skeletal maturation that might be anticipated if a growth-promoting agent such as methyltestosterone had been given. Since the patient was studied for a relatively short period, no conclusions can be made on the ultimate effect of therapy on skeletal maturation.

► [In addition to the other possible adverse effects of systemically admin-

istered corticosteroids, in children the continued and long-term use of these hormones may result in suppression of skeletal growth.

As pointed out in this article, when the corticosteroid is withdrawn there is usually an acceleration in linear growth. According to Blodgett and co-workers (New England J Med. 254:636, Apr. 5, 1956) within few weeks of onset of cortisone therapy there is slowing of statural growth and skeletal maturation. In children with normal endocrine function, minimum of 45 mg./sq. m. body surface area is necessary to reduce the growth rate. If the cortisone is stopped from time to time, the suppressed growth is regained. In this way cortisone may be given for prolonged periods without necessarily altering the child's ultimate stature.—Eds.]

Genodermatoses with Variable Circinate Erythema. A. Bazex and A. Dupré[5] (Toulouse, France) describe a previously unreported dermatosis.

Woman, 49, had skin manifestations which appeared shortly after birth and consisted of variable circinate erythema. It was characterized by bright red, noninfiltrated patches with epidermal collerette, disseminated symmetrically all over the body, coalescing into large plaques of circinate configuration, healing in the center and extending peripherally. Remissions never exceeded 1-3 years. Examination showed fixed erythema in the buccal and mediofacial regions including the nasolabial fold, and also in the perianal-vulvar region. Congenital, universal, persistent hypotrichosis was observed. Alopecia necessitated wearing a wig since the patient was aged 14. Eyelashes and eyebrows were scanty, axillary and pubic hair were defective. Nails, teeth, sweat and sebaceous secretion were normal. No other congenital malformations were found, but mental debility existed.

Histologic examination revealed irregularly fractionated hair medulla and trichonodosis of the pubic hair. The circinate erythema lesions showed moderate hyperkeratosis and acanthosis, small nests of lymphocytic exocytosis and marked vascular congestion with numerous capillaries.

Together with erythrokeratoderma variabilis (Mendes Da Costa), *genodermatosis en cocarde (Degos)* and ichthyotic conditions of the partial erythrokeratoderma type the case described is included in a new group of genodermatoses with variable circinate erythema. All these conditions have the same congenital appearance; they usually occur in females and are variations of the nonpruritic, noninfiltrated lesions associated with mild hyperkeratosis (formation of epithelial fringe, i.e., collerette, or even scales) showing symmetrical distribution, central involution and peripheral enlargement. There is also great variability not only in shape and size but also in duration (months, weeks, days and even hours).

(5) Ann. dermat. et syph. 83: 17, Nov.-Dec. 1956.

Angioma Serpiginosum is reported in 11 cases by W Frain Bell[6] (St John s Hosp for Diseases of the Skin, London) The fundamental lesion is an angiomatous red to deep purple punctum Individual lesions may reach the size of a pinhead but smaller puncta requiring a lens for adequate identification are usually also present. In some cases



Fig 31 (Courtesy of Frain Bell, W Brit J Dermat. 69 251 268, July Aug 1957)

there is a variable degree of background erythema which may be dusky in color and at times accompanied by small groups of minute linear telangiectatic vessels In some areas the minute puncta are grouped while elsewhere they may be isolated singly or in twos or threes in areas of otherwise normal skin Degree of compressibility of the puncta is variable but is at the most only partial and often the color is unchanged by diascopic pressure

(6) Brit. J Dermat. 69:251 268, July-Aug 1957

The active production of puncta is usually gradual al though long quiescent periods may occur The resultant grouped puncta may present in serpiginous, gyrate or linear patterns. Spontaneous partial or complete cure may occur after some years. It is unlikely that atrophy occurs. Purpura is never present. Angioma serpiginosum commonly appears in early childhood. It most commonly affects the lower ex tremities and may be unilateral. Rarely the lesions may be widespread over the trunk and extremit es. About 90% of cases occur in females.

The most frequent h stologic change is dilatation of the small capillaries of the papillary and subpapillary plexus of the dermis, with or without thickening of the vessel wall. There is usually no inflammatory reaction and little or no hange in the epidermis Interpretation of case reports in the literature is difficult but t appears that W se and Pollit zer and Montgomery and Bailey and certain other American cl nicians have a different clinical and histologic conception of angioma serpiginosum.

Girl, 5 first showed reddish discoloration of the skin of the left but tock t age weeks Within few weeks both calves were affected. Fairly rapid spread occurred during the 1st year of life to extensive areas on the back of both lower extremities, the right being more af fected than the left, particularly over the buttocks, upper thigh (Fig 31) and the calf. The lesions consisted of violaceous puncta on dusky erythematous background. I some areas partial fading of the puncta occurred on compression, but elsewhere no change was produced. Numerous discrete puncta were noted over the right pinna and on the right forearm. A lesion on the dorsum of the right foot resembled ordinary nevus flammeus.

Leiner's Disease. Francis W Lynch (Univ of Minne sota) eports a case

Boy aged 3 months, had generalized eruption, with moist, red eczematous reas on the chest. The eruption had appeared on the ab domen at age 2 weeks and had become generalized about 5 weeks later Diarrhea and generalized lymphadenopathy were also present. Soon he as covered by moderately red, large, flaky scales, both dry and moist Diarrhea became more severe, leading to dehydration Un der antibiotic therapy the fever subsided from 104... F to normal but rose again before death about weeks after admission.

Skin biopsy showed parakeratosis, slight hyperkeratosis and ede ma of the papillae. A few lymphocytes wer present in the epidermis and the papillary cutis and perivascularly in the deeper cutis. No specific histologic diagnosis was made. Autopsy was not done.

Review of the literature shows general agreement that

J) A.M.A. Arch Dermat. 7 :9 733, May 1957

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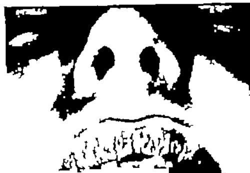
Fig 31 (Courtesy of Frain Bell, W Brit. J Dermat 69 251 268 July Aug 1957)

there is a variable degree of background erythema which may be dusky in color and at times accompanied by small groups of minute linear telangiectatic vessels. In some areas the minute puncta are grouped while elsewhere they may be isolated, singly or in twos or threes in areas of otherwise normal skin Degree of compressibility of the puncta is variable but is at the most only partial and often the color is unchanged by diascopic pressure

(6) Brit. J Dermat. 69:251 268, July-Aug 1957

posure to sun. Only 6.5% of patients failed to respond satisfactorily 44.5% had been previously treated from 6 weeks to 8 years for seborrheic or contact dermatitis.

Cyclic attacks varying from 2 to 10 a year had occurred in 81 patients 4 were seen during the first attack and 7 had had a continuous eruption since onset 3 months to 2½ years previously Of the 86 patients who responded well to treat



F 32.—Papulovesicular plaque [illegible] [illegible] and simulating allergic eczematous (contact) dermatitis. (Courtesy of Frumess, G M and Lewis, H M. A.M.A. Arch. Dermat 75 245-248, February 1957)

ment 63.2% had no recurrence for 4-23 months after termination of treatment.

[It would be better to refer to this interesting clinical picture and series of events as "light sensitive seborrheic-like dermatitis. The use of the suffix "id" is confusing. The evidence that these eruptions ar based on light sensitivity is not yet entirely convincing, despite the good therapeutic effect of antimalarials.—Eds.]

Lymphocytic Infiltration of Skin (Jessner) C. D Calnan[1] (St. J hn s Hosp for Diseases of the Skin, London) presents 7 cases and emphasizes that the condition is not rare. There is a heavy preponderance of males (20 of 21 patients) Usually adults under age 45 are affected The usual sites are the malar region and the back of the chest, but the forehead, neck, mastoid region, arms, legs, chest or abdomen may be invol ed. The lesions re aggregated erythematous papules (Fig 33) or plaques, varying in size from 2 mm. to 2 cm. in diameter and may be arranged n crescents or rings. They a un form rose-pink and there is no scaling or other hange.

The course varied from several months to about 10 years

(1) Brit. J. Dermat. 69:169-173, May 1957

Leiner described a disease different from Ritter's disease and from other exfoliative dermatoses of infancy except possibly severe extensive seborrheic dermatitis and atopic erythroderma. The literature shows several important areas of disagreement (1) Leiner's emphasis on occurrence in bottle-fed babies only conflicts with the experience of others. (2) Leiner's denial of importance of the seborrheic factor is controverted by many authors (3) A possible association with atopy is difficult to evaluate.

The frequent (or obligate) existence of a gastrointestinal disorder and its resistance to treatment are characteristic features of Leiner's disease. Since the dermatologic features are not classic and constant Lynch suggests that it is better to avoid the descriptive title erythrodermia desquamativa, which suggests a dermatologic entity and to use the term Leiner's disease regarding the disease as a reaction or syndrome rather than as a morphologic dermatologic picture. The eruption is neither entirely seborrheic nor entirely atopic, but rather these factors (and perhaps sometimes others) are present in varying degrees in different cases and at different times in the same case

Light-Sensitive Seborrheid is described by Gerald M. Frumess and Henry M Lewis[8] (Univ of Colorado) The eruption involves the face only Sites of predilection are the circumoral nasolabial and nasobuccal areas The eruption occurs in three phases The first phase appears abruptly with patches of closely packed, pointed papules and at times, papulovesicles Pruritus is absent or moderate. The eruption simulates a contact dermatitis (Fig 32) The second phase appears 5-10 days after onset The papules have flattened out and the sites are scaly and erythematous, resembling those of seborrheic dermatitis Seborrhea capitis is invariably present. The third phase is characterized by residual erythema Patients experiencing recurrent attacks may present one phase superimposed on another

The authors found that attacks are precipitated by sun exposure. They observed 92 cases occurring chiefly in women in the ratio of 19 1 In 3 of 5 men fluorescent lights were the trigger agent

Treatment consisted of topical applications for seborrhea capitis antimalarial drugs internally and prevention of ex

(8) A.M.A. Arch. Dermat. 75:245-248, February 1957

posure to sun. Only 6.5% of patients failed to respond satisfactorily 44.5% had been previously treated from 6 weeks to 8 years for seborrheic or contact dermatitis.

Cyclic attacks varying from 2 to 10 a year had occurred in 81 patients 4 were seen during the first attack and 7 had had a continuous eruption since onset 3 months to 2½ years previously Of the 86 patients who responded well to treatment 63.2% had no recurrence for 4-23 months after termination of treatment.



Fig. 32.—Papulovesicular plaques involving perilabial areas and simulating allergic eczematous (contact) dermatitis. (Courtesy of Frumess, G. M. and Lewis, H. M.: A.M.A. Arch. Dermat. 75:245-248, February 1957.)

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Lymphocytic Infiltration of Skin (Jessner) C. D Calnan[9] (St. John's Hosp for Diseases of the Skin, London) presents 7 cases and emphasizes that the condition is not rare. There is a heavy preponderance of males (20 of 21 patients) Usually adults under age 45 are affected. The usual sites are the malar region and the back of the chest, but the forehead, neck, mastoid region, arms, legs, chest or abdomen may be involved. The lesions are aggregated erythematous papules (Fig 33) or plaques, varying in size from 2 mm. to 2 cm. in diameter and may be arranged in crescents or rings. They are a uniform rose-pink and there is no scaling or other change.

The course varied from several months to about 10 years,

(9) Brit. J. Dermat. 69:[illegible]-171, May 1957

with recurrences and remissions Most patients showed periods of freedom of a few weeks or months but none recovered permanently Therapy was not beneficial, most apparent improvement probably representing spontaneous remission.



Fig. 11.—Typical appearance of aggregated papules over symmetric area in case of lymphocytic infiltration of skin. (Courtesy of Calnan C. D. Brit. J Dermat. 69: 169-173 May 1957)

No case has been reported to progress to lymphoblastoma or leukemia

Histologically the epidermis is normal. The entire network of vessels is enveloped in a dense mantle of lymphocytes. The process may extend down to the fat, and the tissue spaces of the dermis may also be permeated with lymphocytes. When the face is affected clinical diagnosis is usually papular lupus erythematosus or a light eruption When lesions are on the body diagnosis is often reticulosis or annu

lar erythema. The most regular features that help in differentiation are uniform rose-red color and the fact that the lesion consists entirely of erythematous papules which may be discrete or grouped into plaques crescents or rings.

Histologically sarcoid and syphilis can be excluded. Though the arrangement of the infiltrate is compatible with lupu erythematosus, absence of epidermal changes speaks against this condition. W thout clinical data it is impossible to exclude early lymphocytic reticulosis or one of the annular erythemas

► [The concept of lymphocytic infiltration of the skin is a distinct contribution, especially to differential diagnosis of lupus erythematosus and other eruptions of the face which consist of infiltrated lesions. None of the cases which have been under our car and which fitted in clinically and histologically with Jessner concept, on further observation has turned out to be lupus erythematosus or light-sensitive eruptions or leukemias or any other dermatosis which formerly would have been considered.—Eds.]

Subacute Hypodermic Nodules of Vascular Origin may be d vided into two poorly distinguished groups according t J Hewitt (Paris) The first includes erythema indura t m of Bazin which occurs predominantly in women The nodules are purplish, show prolonged attacks of activity in winter and often ulcerat The tuberculous nature of Bazin s d sease is difficult to pro because it is a nodular vasculit s in the broadest sense of th term Peripheral vascular upsets are often p esent and cold often plays a part The tubercle ba ll attacks the endothelium of the subdermal blood els by a process that is probably allergic This explains why specif c antituberculou therapy is often ineffecti e while itamin C nd vasod lators more often succeed Other bacteria, especially treptococci may be respons ble for some case f erythema induratum

I the second group of hypoderm c ascula nodules the lesion are mo nflammatory than in erythema nduratum S me are very milar to erythema nduratum and may ul erat Oth rs are mor superficial with a mor intense dermal in olvement and a more cute course Subacute inflammatory plaques may be associated with th nodules which ften small and variable in umber This mor nflammatory group of hypoderm c nodules corresponds to the nodula scul ti of Montgomery and O Leary

A abnormal con titutional vascula terrain seem to be ommoner tha m typical erythema duratum The nodules

(1) Brit J Dermat 60 2 3 290, July Aug 17

may often be of streptococcic origin. As in erythema induratum the mechanism is likely to be allergic in character The intradermal reaction to a stock antistreptococcus vaccine and the antistreptolysin titer may be of diagnostic value.

Whatever the precipitating cause, peripheral vascular disorders are important in many patients with hypodermic vascular nodules Bed rest and vasodilators offer the best treatment when vascular lesions seem to be primary and, of course for cases of thrombophlebitis that involve the large veins It is important to eliminate by thorough investigation, all blood-borne factors that may excite vascular reactions in a favorable soil

Dermatitis Nodularis Necrotica. G W Binkley[2] (Western Reserve Univ) reports a case.

Man 30 white had skin eruption of 14 years duration. When first examined he had comedones, pustules and small furuncles on the face,



Fig 34 —Nodules and pustules in case of dermatitis nodularis necrotica. (Courtesy of Binkley G. W A M A. Arch. Dermat. 75 387 393 March, 1957)

back and extensors of the forearms. The legs showed hard round, red nodules ranging in size from several millimeters to 1.5 cm. (Fig 34) In their centers were small yellow summits or craters. On the posterior and lower third of the left leg was an irregularly shaped ulcer with necrotic base. Around the ulcer were discrete follicular pustules.

Cyclically the skin showed pustules and acneform papules on the face and back clear superficial vesicles deeper intradermal pustules, telangiectasia and purpuric lesions on extensors of the upper and lower extremities the palms, soles and buttocks. At first, a diagnosis of iododerma bromoderma or dermatophytid was considered, but be-

(2) A M.A. Arch. Dermat. 75 387 393 March, 1957

cause of the repeated flares followed by almost complete remissions, a diagnosis of dermatitis nodularis necrotica was made.

An abundance of Staphylococcus pyogenes colonies was isolated repeatedly from the surface of the skin and nasal vestibule, but no organisms were found in intact vesicles and pustules or on blood culture. Local and systemic antimicrobial therapy was of no value. Cortisone was not beneficial, but corticotropin given for 3 months produced a complete remission that has persisted for several months.

The site of the tissue reaction in dermatitis nodularis necrotica can be the superficial epidermis upper dermis, pilosebaceous stru tu e and vessels of the dermis In the present case, subcutaneous injection of autogenous Staph. pyogenes vaccine and stock staphylococcus ambotoxoid produced no unusual reaction and no clinical benefit. Vaccines prepared from stool cultures, on the oth r hand, delayed severe local eactions 4-9 hours after injection, but a polyvalent vaccine of these organisms given for 6 weeks did not produce improvement. On intracutaneous injection of the vaccine there was no immediate local wheal or flare, but 4-24 hours later there were red, elevated nodules at the sites similar to certain of the nodules of dermatitis nodulari necrotica. Intra enou injection of typhoid-paratyphoid vaccine resulted in high fever for 4 days, development of superficial vesicles and progression of th deep ulcers of the legs. In view of these re lts with vaccines, dermat tis nodularis necrotica may be a continuous state of the Sanarelli Shwartzman reaction. The preparatory bacteri m in this case may have been the ubiquitous surface Staph. pyogenes and the reacting factor may ha e been coliform bacteria.

Degos Malignant Atrophying Papulosis Anatomic and Clinical Study A Basset, R. Guilaine and J Montfort[1] (Paris) present the eighth case to be reported since the origi nal descript on of thi disease n 1942.

Boy 16 had a peculiar skin eruption for 8 months First lesions appeared, without generalized illness, on the lateral surfaces f the neck and anterior thorax, consisting f reddish, hemispheric, lentil-sized papules, which were slightly edematous and accompanied by mild itching After 4 or 5 days, the papule became umbilicated, with the central depression covered by small scale, which was easily removed, followed by rapid atrophy of the porcelain type. The peripheral portion formed an edematous cushion, with fine telangiectasia. The entire lesion was firm. The peripheral infiltration then slowly subsided, lea ing small honeycombed scar The lesion developed to its height in about 3 weeks, and cicatrization took place in bout 6 months.

(1) Presse méd. 64: 2193 2194, Dec. 21, 1956.

The patient's admission coincided with the appearance of abdominal symptoms, consisting of postprandial pain in the right iliac fossa and emission of liquid stools, especially at night. The skin lesions then were predominantly on the trunk. On the extremities they were principally proximal involving the flexor surfaces (Fig 35) The face, palms soles and mucosae were spared.

Histopathologic study of the skin showed a cuneiform lesion whose peak corresponded to a degenerated arteriole in process of separation from the subdermal plexus and rising toward the subpapillary plexus.



Fig 35.—Lesions in pectoral region. Note papular lesion and edematous condition of internal surface of arm. (Courtesy of Basset, A et al Presse med. 64:2193-2196, Dec 25 1956.)

The deep dermis was the site of fibrinoid necrosis and endothelial and subendothelial proliferation, accompanied by fresh thrombosis and signs of initial repair. The internal elastic layer appeared intact. The media and adventitia were not involved. In the middle and superficial dermal layers where the vascular structure is transitional, fibrinoid lesions involved the entire wall and extended into the perivascular collagen, but without cellular reaction. At the edge of this cuneiform lesion there was a vascular reaction with capillary dilatation and lymphohistiocytic infiltration. As a whole the lesion was a white cutaneous infarct corresponding to a thrombosing fibrinoid endarteriolitis.

Synthetic anticoagulants and ACTH perfusions produced only

pseudo improvement. The patient lost weight rapidly and deterioration of his general condition was punctuated by two severe abdominal attacks with bloody diarrhea, week apart. Death occurred 10 days later little over a month after admission.

Besides generalized peritonitis, autopsy revealed lesions of three types (1) perforations, the largest (about 5 cm.) involving the posterior surface of the stomach near the inferior antral border with 2 smaller perforations in the small intestine (2) 2 thrombotic ileal infarctions, the larger extending 30 cm. and involving most distal loops and the smaller involving the vertical proximal portions and (3) about 20 small, mummular subserous plaques in the small intestine and colon. Histologic study of two nonperforating intestinal lesions showed extensive necrosis, predominantly mucosal, infiltrated by polymuclears, corresponding to thrombosing endarteriolitis in submucosa and subserous layers.

Degos malignant atrophyi g papulosis seems to affect principally young males, aged 15-25 although the original patient was 49 and another (a man) was 59 The basic lesion is an edematous papule evolving secondarily toward central atrophy Lesions are not always rounded some are oval elongated or even angular Some months after onset of skin lesions an acut malignant abdominal complication appears This has occurred as late as 3-6 years, but in most cases 1½-10 months after the skin lesions appeared. The ascular origin of th abdom nal lesions may be suspected by slight hemorrhage. Th enterorrhagia in the present case was duplicated n o e other and hematemesis has also been reported. Emergency operation on 4 pat ents revealed peritonit s, but the perforation was so small that it was found and repaired in only 1 patient, who survi ed 1 month and then d ed after second perforation.

The histologic fi d ng of obliterating arteriolitis at the peak f th lesion is the leading diagnostic feature. Intestinal lesions studied in 5 cases are unquest onably similar on sting of whit infarcts in terminal vessels caused by fibrinoid thrombosing endarteriolitis.

Ubiquity of the pathologic processes opposes rigid classification of the disease Some pathologists egard these le sions s related to thromboangiitis obliterans. Despite the p sence of fibrinoid in the ascular lesions, the linical findings merit class fication of this syndrome as a separate entity

► [A rare but characteristic syndrome T our knowledge, no typical case ha been reported from the North American continent.—Eds.]

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Synthetic anticoagulants and ACTH perfusions produced only

not exist in the necrobiotic area which extended down to the hypoderm, but at the borders of this area few discrete lymphocytic infiltrates were seen. Inflammatory infiltration with marked endangiitic changes was also present in the intima of the arteries and veins.

Thromboangiitis cutaneointestinalis disseminata shows first a completely benign course, becoming malignant when analogue changes occur suddenly in the intestinal walls, causing abdominal pains, vomiting, ileus and eventually death. Onset of cutaneous manifestations and intestinal involvement varies from a few weeks to 3 years. In the patient described, who has been under observation for nearly 3 years no intestinal manifestations have occurred thus far

Erythema Neonatorum Allergicum Study of Incidence in 200 Newborn Infants and Review of Literature. William B Taylor and Charles P Bondurant, Jr* (Univ Hosp Ann Arbor Mich.) point out that erythema neonatorum allergicum is a dermatitis of the newborn infant, consisting of ery



Fig 17 —Erythema neonatorum, close up. (Courtesy of Taylor, W. B. and Bondurant, C. P., Jr.: A. M. A. Arch. Dermat. 76: 591-594, November 1957.)

* A. M. A. Arch. Dermat. 76: 591-594, November 1957

Malignant Atrophic Papulosis (Thromboangiitis Cutaneo-intestinalis Disseminata) H Stauffer and G Miescher[4] (Univ of Zurich) report a recently observed case of this rare condition

Man, 23 in 1953 had a cutaneous eruption of disseminated small papules on the trunk and later on the extremities. His general condition was normal The papules were first hempseed-sized, skin colored to pale red, and later became pinhead or lentil-sized, porcelain



Fig 36.—Lesions in right upper abdominal region. (Courtesy of Stauffer H and Miescher G Hautarzt 8 4-7 January 1957)

white in color with a central dimple-like, occasionally hyperkeratotic, depression the peripheral zone was slightly raised, infiltrated, pale red and sometimes finely telangiectatic (Fig 36) Subsequently the lesions showed involution with pigmentation the larger ones often exhibiting a central necrosis which healed with scar formation. The eruption proceeded by attacks in which a single lesion or a few lesions appeared. No other clinical findings existed. The hemogram, blood

Oct C R S

(4) Hautarzt 8 4-7 January 1957

planation has been found for the bilaterality and symmetry with which the lesions are grouped.

The condition is comparatively common in Cuba, Puerto Rico and Jamaica and probably also in other places where the climate is hot in cold or temperate climates however it is rarely seen White men n the second to fourth decades engaged in griculturul work, chiefly on sugar plantations, are the persons most commo ly affected in Cuba, and since the lesions which appear principally on the legs are aggravated by heat and sweating during hard work, the condition is often incapacitating and can be classed as occupational. Many forms of treatment have been used during the years ranging from the topical appl cation of various drugs to the admi istration of antibiotics and cortisone derivatives but none ha e proved defin tely curative and the patient is often forced t accept a change of occupation

Apart from the fact that most of the pat ent in th series had a diet poor in proteins fats and fresh vegetables that they were often affected by intestinal parasites and digesti e disturbances of a funct onal character and that in many cases they had foci of nfection n the teeth, tonsils, sinuses d other paranasal structures, th most n ticeable feature f their general cond tion was the high percentage of aller gi cond tions, such as asthma, urticaria, coryza, dermatitis a d intolerance fo certain foods, drugs and other substan es found in their personal and family histories

Cutaneous Reactions to Embedded Extraneous Hair Extra eous ha r is capable of penetrating skin and acting as a foreign body These l sions are more prevalent than the few reported cases would d cat M chael J Scott (Seattle) de scribes i types of eaction occurring after hair penetration

M mal reactions may occur w th no gros defect discern ble There may be ntermittent tenderness or pain with pressure in a area of apparently normal kin The offend g ha may protrud or may have disappeared. Paring the tender area ften reveals the ha as a minute dark peck

Hair w th mascara dye or other foreign material are most pt t produce abscesses Subsequent purulent dra nage of ten d lodges the hair a d spontaneous healing result Repeated episodes of quiescence nd suppuration may occur over con iderable period.

M rch Dermat. 39 2, July 1 57

thema papules and pustules that appear in the first 3 days of life and disappear by the 6th day Only about 10% of the cases are severe enough to present pustules. The lesions may appear anywhere on the body but the anterior trunk (Fig 37) is the commonest site The pustules are sterile and contain over 90% eosinophils The importance of the eruption lies in its high incidence and its recognition and differentiation from potentially serious cutaneous disorders affecting the infant In its severest form that of pustule formation, the eruption may be differentiated from the pyodermas by stained smear of the pustule fluid and by bacterial culture

Of the 200 consecutive newborns observed 62 (31%) had erythema neonatorum allergicum during their hospital stay 13 (6.5%) had only physiologic postnatal redness and 9 (4.5%) had mere dryness and scaling of the skin The eruption appeared on the 1st day after birth in 37% and on the 2d day in 60% It lasted 2 days or less in over two thirds of the patients. The anterior trunk was affected in 77% posterior trunk in 31% face in 26% and extremities in 1/%

► [An article on the same subject by Harris and Schick (A.M.A J Dis Child. 92 27 1956) appeared in the 1956-57 YEAR BOOK. At that time, we questioned the allergic etiology of this disorder and the present paper does not furnish additional evidence in favor of an allergic origin. The pathogenesis of this disease has yet to be ascertained.

Recently Eitzman and Smith (A.M.A. J Dis. Child. 94 484 1957) demonstrated that infants between 36 hours and 21 days of age respond to nonspecific inflammation with an eosinophilic exudate. The eosinophil counts varied from 10% to 93%—Eds.]

Depilating Folliculitis of Smooth Skin (Arnozan and Dubreuilh) Pastor Fariñas and V Pardo Castello[6] (Havana) base their account of this condition first reported by Arnozan and later described histopathologically by Dubreuilh on 78 cases observed at Calixto Garcia Hospital during 1937 56. Depilating folliculitis like the other forms of folliculitis resulting in atrophy or destruction of the pilosebaceous follicle, is a follicular and perifollicular inflammatory process that completely destroys the cutaneous papilla causing permanent alopecia and leading to the formation of cicatricial tissue. The lesions which tend to appear in bilateral symmetrical rows or groups are due to staphylococcic proliferation within the follicular ostium after it has become occluded by a keratotic plug Bacterial studies invariably reveal the presence of Staphylococcus aureus in pure cultures No ex

(6) Bol. Soc cubana dermat. y sif. 14 7 4 31 June 1957

hairs are preserved because they are too short to be gathered by the hair fasteners (Fig 38)

Close inspection often reveals patches of follicular atrophy and at times scattered folliculitis or perifollicular erythema. In the incipient stages, the patches of *folliculitis* may be closely grouped with firmly adherent crusts or scales suggestive of seborrheic eczema. Once the hair has been shed and the trauma thus removed, the folliculitis heals but the fol



Fig 38 (Courtesy of Hjorth, N Brit J Dermat 69 11 322, September 1957)

licles undergo trophy and cicatricial alopecia gradually develops Cha ging the ha style usually results in enewed growth of hair but f f llicular trophy is advanced, th hair loss may be permanent.

Sequelae to Cold Injury in 100 Patients Follow-up Study Four Years after Occurrence of Cold Injury in service men evacuated from Korea during the winter of 1950-51 is presented by Joseph R. Blair Richard Schatzki and Kenneth D Orr* Cold injury was classified into 4 degrees of severity 1st, n l ng only hyperemia and edema 2d, hyperemia

) J A M A 43 203 1296, Apr 19

Sinus formation occurs most often in the interdigital webs of the fingers but may occur elsewhere. It is noted fairly often in barbers. The sinus may be asymptomatic for years. Usually there is a minute opening through which loose hairs can be expressed. Intermittent scanty purulent discharges may occur.

Repeated episodes of inflammation and suppuration may result in formation of a foreign-body granuloma. The clinical appearance of these lesions is nonspecific and variable. Some are elevated, others are subcutaneous and detectable only on palpation. Sites of predilection are the hands, feet and the genital area. On the plantar surface, the lesions may resemble plantar warts.

Miscellaneous reactions, such as paronychia, onycholysis, conjunctivitis and phimosis, may result from penetrating hair. Combinations of the previously described reactions may occur. Sinus formation may be associated with abscess or foreign body granuloma. Abscess formation and foreign-body granuloma often occur together. The combination of a small sinus tract and abscess formation in the postauricular region clinically resembles an infected sebaceous cyst. Many other combinations are possible.

In early lesions, removal of the offending hair is curative. Treatment of deep abscesses, sinuses and deep granulomas requires surgery. Total excision or incision and curettage of the sinuses and granulomas often is necessary.

► [Embedded hair may play a role in the pathogenesis of skin lesions more often than one would think. The possible mechanism of penetration of extraneous hair into the skin is discussed by Schulze (Arch. Dermat. & Syph. 61:668, 1950) and Leider (A.M.A. Arch. Dermat. 76:501, 1957). The latter showed how an ordinary straight pin can be driven through a metal coin.—Eds.]

Traumatic Marginal Alopecia. Special Type: Alopecia Groenlandica. Niels Hjorth[1] (Finsen Inst., Copenhagen) reports 11 cases of traumatic hair loss in young girls induced by the "ponytail" hair style. The cause is constant traction on the hair. The chief sign of traction alopecia is symmetrical baldness or thinning at the hair line. As a rule, the lesion is localized to the temples, but it may also affect the back of the head, the forehead or the parting, depending on the hair-dressing style. A characteristic finding is a thin straggly strip of hair at the distal margin of the alopecia where the

(1) Brit. J. Dermat. 69:319-322, September, 1957.

Osseous X-ray Findings in Ulcus Cruris are described by Oscar Gilje and Ivar Andresen[1] (Rikshosp., Oslo) to determine the frequency of osseous alterations, their connection with leg ulcers, the nature of the osseous process and relation between localization of the ulcer and extent of osseous change. Of 87 men and 142 women, 127 had varicose ulcers, 68 with postthrombotic and 34 with arteriosclerotic affections. There were positive x-ray findings in 134 patients.

Osseous changes also developed in patients with eczema, edema and induration. Various forms of periosteal reaction were seen from a fine wavy line to thick, sclerotic formations of new bone giving the bones a ragged or fringed appearance. The changes which are due to osteoporosis, osteosclerosis and proliferation of the periosteum may extend along the entire length of the tibia and fibula into the ligamentum interosseum. The severest reactions occur in patients with ulcers of longest duration. They are most pronounced in the ulcer region but do occur in other parts of the bones. Often both tibia and fibula are involved, but if only one, it is usually the fibula. No changes have been seen in healthy legs.

It is assumed that ulcers, eczema, edema, infiltration and the roentgenologically demonstrable changes in the skeleton all have the same etiology and pathogenesis, i.e. a circulatory insufficiency and that the osseous alteration and alteration in the soft tissues and ulcer are parallel phenomena.

► [In view of the high incidence of roentgenologic findings in these patients, it seems surprising that clinical difficulties due to bone or periosteal involvement have not been observed at least in some of the cases.—Eds.]

Rheumatoid Arthritis with Chronic Leg Ulceration. J. H. Allison and F. Ray Bettley[2] (Middlesex Hosp., London) observed 6 patients with similar clinical pictures. All had severe crippling and apparently typical rheumatoid arthritis with many subcutaneous nodules. In 4 patients, the ulcer was on the lower third of the leg, in 1 just below the knee and in 1 on the foot. Onset was not observed. In 1 patient, an ulcer was noted only 3 weeks after it appeared. It was already deeply punched out, about 1.5 cm. in diameter, with smooth regular edges. There was no slough and the floor appeared to be formed by subcutaneous tissue. Around the ulcer was a dark red flush, with only little palpable induration and no edema. Larger ulcers retained these characteristics. Pain

(1) Acta dermat.-venereol. 36: 294-302, 1956.
(2) Lancet 1: 288-290, Feb. 9, 1957.

with vesicle formation 3d necrosis of skin and subcutaneous tissue and 4th complete necrosis and loss of tissue. Symptoms 4 years after frostbite in order of frequency were excessive sweating pain cold feet numbness, abnormal color and symptoms in the joints Subjective complaints generally were more severe than would be expected from the physical appearance and except for hyperhidrosis, were more severe in winter than in summer

In 1st and 2d degree injury the only physical findings were hyperhidrosis occasionally abnormal color of the feet and some joint stiffness Third and 4th-degree injury caused areas of scar formation and skin thickening abnormal nails tissue deficit or actual tissue loss (in 4th-degree cases) color changes, especially depigmentation in the Negro joint pathology and growth disturbance (when the injury occurred before closure of the epiphyses) In more than two thirds of the patients in whom injury was severe enough to involve full-skin thickness the nails were abnormal They were extremely thickened heavily ridged and contracted at the front margin Often the nail beds were cyanotic.

Hyperhidrosis was determined qualitatively by palpating the feet 10 minutes after drying them with a towel In many patients, the feet were quite wet after 10 minutes had elapsed. It is not known whether this hyperhidrosis is a cause or effect of cold injury A hyperhidrotic person is a likely candidate for cold injury Hyperhidrosis may have been present before the frostbite occurred and may have been a major factor in causing it

Abnormal color in white patient was primarily an erythrocyanotic appearance probably associated with peripheral circulatory disturbance In the Negro abnormal color was caused by depigmentation which occurred in all Negroes with 3d and 4th-degree frostbite Depigmentation was similar to that noted in the Negro after skin burns Scars after 3d-degree injury had a punched-out appearance resulting from sloughing of the skin and subsequent granulation of the lesion Fourth-degree frostbite produced extensive scarring and occasionally mutilation of terminal phalanges.

► [Cold injury was an important and troublesome problem in World War II and in Korea over 100 000 United States soldiers had such injuries. As pointed out, sequelae can be severe with permanent tissue changes, deformity and even loss of parts.—Eds.]

mis there are none of the irregularities and nuclear abnormalities noted in the malignant type. The distinctive feature is found in the corium—an inflammatory infiltrate consisting almost entirely of plasma cells. The capillaries are dilated and their walls thickened. There are abundant deposits of hemosiderin as shown by prussian blue staining. In differential diagnosis, conditions to be considered, in addition to the malignant form are psoriasis, lichen planus, eczema, diabetic vulvitis or balanitis and the genital disturbances observed in the menopause or after ovariectomy as well as the disease described by Sulzberger and Garbe. In general, the picture is not consistent with syphilitic etiology. From the standpoint of nosology benign erythroplasia must be differentiated from the malignant form on the basis of distinctive histologic features.

► [In an article by Sulzberger the junior editor and Hunt (A.M.A. Arch. Dermat. 73:101, 1956) it was concluded that erythroplasia of Queyrat and Bowen disease of the glans are one and the same disease.—Eds.]

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5 CANCERS, PRECANCEROSES, *OTHER TUMORS*

Malignancies of Scalp with Invasion of Skull and Intracranial Space: Report of Four Cases with Necropsy Verification; presented by Cyril B. Courville[4] (Los Angeles County Hosp.)

CASE 1.—Woman, 28, had squamous cell carcinoma of the parietal scalp. The lesion recurred after two operations. Within 16 months there was a huge, ulcerating and bleeding lesion that eroded the underlying bone to invade the regional dura mater, leptomeninges and brain. It had provoked left exophthalmos and ultimately extended into the temporal muscle, parotid gland and neighboring soft tissues. Death occurred from inanition.

CASE 2.—Woman, 72, had carcinoma of the skin of the frontal region. Surgery was refused. The lesion eventually broke down to form a huge shallow crater exposing the eroded external table and breaking through into the intracranial space over the left frontal lobe. The ulcer became infected and infested with maggots, which also invaded the secondary frontal abscess. Death occurred 2 years after onset.

CASE 3.—Woman, 49, had a lump in the occipital scalp which proved to be a metastatic spindle cell sarcoma with the primary lesion in the retroperitoneal region. The scalp growth was removed, with subsequent recurrence demanding a second surgical intervention.

(4) Bull. Los Angeles Neurol. Soc. 21:142-74, December 1956.

was a constant feature and sometimes was severe. Varicose veins antecedent phlebitis and other evidence of vascular stasis in the legs were not observed.

In 4 of the 6 patients L.E cells were found Four had drug eruptions in the past Many other symptoms of great variety were all compatible with a diagnosis of disseminated lupus erythematosus Histologic studies suggest that collagen necrosis may be the primary lesion It may be of course that the primary lesion in the skin is the same as that which originates a rheumatic nodule in the deeper tissues, forming an ulcer in the 1 case and a proliferative tissue reaction in the other The fact that all 6 patients had subcutaneous nodules is unusual because incidence of these nodules in rheumatoid arthritis usually is about 20%

There is great difference between the present cases and the more acute syndromes noted in disseminated lupus erythematosus even though the underlying pathologic mechanism may be closely similar All of these patients are running a chronic course and in only 1 has general health been affected. The ulceration in these patients failed to respond to ordinary local treatment but in 3 patients recovery followed steroid therapy

► [It is interesting that the ulcers of only some of the patients treated showed a favorable response to corticosteroid drugs. The variety of ulcers of the lower extremity is great, the therapeutic approaches are many and the problems concerning successful management are still numerous.—Ed.]

Benign Plasma Cell Erythroplasia a diagnosis that permits conservative treatment in contrast to the malignant erythroplasia of Queyrat is discussed by Georges Garnier[3] (Paris) The lesions, which can occur at any age, usually involve the mucous membrane of the glans and prepuce. However in 2 cases reported by Garnier the vulva was affected. The lesions are bright or dull red patches of mucous membrane with a varnished appearance as though lacquered. There may be an ecchymotic tint In benign erythroplasia, the patches are irregular ragged and indefinite in outline as contrasted to the sharp delineation in malignant erythroplasia. Usually the patches are asymptomatic although patients may complain of tenderness or pruritu The course is chronic.

Histologic features of benign erythroplasia are moderate acanthosis and intra and extracellular edema in the epider

(3) Brit J Dermat. 69:77-81 March, 1957

nodules which clinically looked like metastases. Besides, on the back of both hands and on the volar aspect of both forearms, solitary or multiple com- to palm-of-hand-sized, pigmented and hyperkeratotic patches had developed which clinically were acanthosis nigricans.

Histologically the tumor was situated in the corium, not extending into the subcutis and consisting of fibromatous and polymorphocellular sarcomatous parts. I the latter cells, the nuclei were often pyknotic, rying in size and occasionally gigantic with numerous mitoses. Many giant cells were seen in the central areas. Silver impregnation showed marked gitterfasern. The collagen fibers were increased, notably in the cicatricial areas.

A nodule excised from the patient's arm, which clinically appeared to be metastatic, showed the structure of dermatofibrosarcoma protuberans. In the peripheral part of the nodule in several vessels, blastomatous cell accumulations were seen growing through the vascular wall, indicating hematogenous origin.

Biopsy of skin tissue f om the back of the left hand disclosed the characteristic structure of acanthosis nigricans w th papillomatosis, acanthosis, hyperkeratosis and melanin increase mainly in the basal cell and in the papillary layer in which there was minor perivascular infiltration.

The 17-ketosteroid excretion was 14.4 mg./24 hours (normal for women is 8-10 mg./24 hours).

Th patient described is the first in whom acanthosis nigricans occurred during the course of dermatofibrosarcoma protuberans with multiple cutaneous metastases. The latter is a less malignant m re superficial type of skin sarcoma according to Gent le, who rather doubted the existence of cutaneous metastases i dermat fibrosarcoma protuberans. In the described histologic changes of an apparently metastatic cu taneous nod le the findings of intravascular blastomatous cell accumulations growing through the vascular wall point to th hematogenous origin and the metastatic nature of the nodule.

The 17-ketostero d excretion was high but not abnormal enough to assume hyperfunction of the hypophysis-adrenal system to be a causati e factor f acanthosis nigricans. Met ab lic products of the tumor and its metastases may explain the cutaneous ymptoms, particularly the pruritus and neurodermitis-like lichenification.

Involvement of Skin in Renal Carcinoma. Report of Two Cases with Review of Literature is ummarized by Albert I Rosenthal and W lter F Lever[4] (Massachusetts Gen'l Hosp., Boston). In the first case the cutaneous lesions were true meta tases. Ther were many firm intracutaneous nod

[4] A.M.A. Arch. Dermat. 7 96-103, July 1957

Death occurred 16 months after the first removal. The skull beneath the scalp tumor was severely eroded, but the growth did not penetrate the dura mater leptomeninges or brain.

CASE 4.—Man, 53 showed lymphosarcoma of the scalp consequent to local injury A firm nodules in the scalp appeared a few days after injury Diagnosis was established by biopsy and radiation therapy was not beneficial A dark, ulcerated area with indurated border developed and death occurred 18 months after injury from inanition and widespread metastasis to the viscera and regional and distant lymph glands. Some involvement of the cranium had occurred secondary to involvement of the pericranium. The intracranial space had been invaded, apparently via the parietal emissary veins. The dural sinus, leptomeninges and cerebral cortex were involved.

After personal observation of Case 4 Courville searched the records of 55 000 autopsies at the Los Angeles County Hospital during 39 years and found only 3 other examples of malignant scalp tumor with secondary erosion of the skull and invasion of the intracranial space Such growths apparently involve the periosteum and then extend into the bone along the small blood vessels penetrating the outer table of the calvarium. The dura usually forms a substantial barrier but is not infrequently invaded as a late development as are the leptomeninges and cerebral cortex. Reports of 10 other cases were found in the literature

Acanthosis Nigricans Associated with Dermatofibrosarcoma Protuberans with Multiple Cutaneous Metastases. Review of the literature show that the malignant type of acanthosis nigricans is associated with cancer of an internal organ usually with stomach adenocarcinoma and less often with adenocarcinoma of the breast lung and bronchus. N Melczer and C Dvorszky[3] (Univ of Pécs) report a case in which acanthosis nigrican followed dermatofibrosarcoma protuberans with multiple cutaneous metastases

Woman, 29 for some years had a molelike lesion which became ulcerated and slowly enlarged after trauma. Examination in November 1954 revealed on the back adjacent to the posterior axillary line a prominent, bluish red, pigmented, small-apple-sized tumor which showed cicatricial contraction in some places. Some lymph nodes of the left axilla were slightly enlarged the cervical lymph nodes were not palpable. X ray examination of the lung carried out because of dyspnea was negative. Clinically, the tumor was assumed to be dermatofibrosarcoma protuberans. Surgical removal was recommended but refused by the patient, who was discharged. On readmission in March 1956, she had intense pruritus and showed lichenified neurodermitis-like plaques on the trunk and limbs. The tumor was not much larger but there were 46 bean to almond-sized firm disseminated

(3) Hautarzt 8:54 58, February 1957

nodules hich clinically looked like metastases. Besides, on the back of both hands and on the olar aspect of both forearms, solitary or multiple com- to palm-of hand-sized, pigmented and hyperkeratotic patches had developed which clinically were acanthosi nigricans.

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Involvement of Skin in Renal Carcinoma Report of Two Cases with Review of Literature is summarized by Albert I Rosenthal and W lter F Le er[4] (Massachusett Gen'l Hosp Boston) In the first case the cutaneous lesions were true metastases. There were many firm, ntracutaneous nod

(4) [illegible] Arch. Dermat. [illegible] 96-102, July 1957

ules on the scalp neck, chest back forehead and thighs Several of the nodules became ulcerated On the trunk were several well-circumscribed subcutaneous masses measuring up to 2 cm in diameter Histologic examination showed extensive infiltration of the skin with masses of epithelial cells In many areas the cells were arranged in lobules or tubules surrounded by a thin layer of collagen (Fig 39) There were foci of necrosis of the tumor cells and extensive infiltration of the tumor masses by polymorphonuclear leukocytes

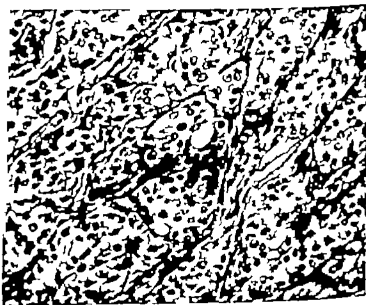


Fig 39 —Cutaneous nodule in case of renal carcinoma, showing arrangement of tumor cells; reduced from × 400. (Courtesy of Rosenthal, A. L., and Lever W F A.M.A. Arch. Dermat. 76 96-102, July 1957)

In some areas the tumor masses invaded and destroyed the epidermis, whereas in others the tumor extended into the deeper portions of the dermis and subcutaneous fat.

In the second case a renal carcinoma extended directly to the skin in the vicinity of a nephrectomy scar It had spread to the skin largely via the blood vessels since histologic examination showed numerous dilated capillaries filled with tumor tissue.

Among 1,312 cases of renal carcinoma reported in 21 large series the skin was involved in 37 (2.8%) Including single case reports, the skin was involved in 69 cases of kidney carcinoma. Of these, 44 patients had true metastases 16 had

extension of the tumor to the nephrectomy scar with no other cutaneous involvement and 9 extension to the external genitalia.

Cutaneous metastases may be extensive or few in number Occasionally there is a solitary metastasis. The head, especially the scalp is a common site of cutaneous metastasis and may be the only area affected. The lesions may be intracutaneous nodules or large areas of subcutaneous infiltration. The cutaneous lesions may show deep brownish to black pigmentation because of the presence of large amounts of hemosiderin. In about 20% of reported cases cutaneous lesions occurred before diagnosis of the primary renal tumor was made.

► [Another instance where the presence of skin lesions can suggest the presence of internal carcinoma before other signs or symptoms of the latter are evident.—Ed.]

Subpleural Pulmonary Metastases in So-called Basal Cell Carcinoma are reported by G Richter

Man, 71, in 1949 received x ray therapy for a scrotal tumor On first hospitalization in 1951 be had several ulcerated basaloinas on the penis and scrotum, which were cauterized with zinc chloride. On his second hospitalization in 1952, multiple basalomas were seen in the genital region along with erysipelas of the buttocks. Irradiation (Chaoul method) was applied to the genital region. Metastases on the left thigh were removed by cautery On the third hospitalization in 1953, the ulcers of the scrotum and inguinal region were larger on the left thigh below Poupart's ligament and hip, new hard, hazelnut-sized nodules existed and the entire left extremity and glans penis were swollen. Treatment included Chaoul irradiation, antibiotics and local therapy The fourth hospitalization occurred in 1954, at which time new ulcerated lesions were seen in both groins and in the proximal areas of the thighs. Four ulcers were destroyed by cautery after which Chaoul irradiation and 0.1% colchicine ointment were applied locally

The patient died in June 1954 at age 76 of pneumonia and heart failure.

Autopsy disclosed multiple basal cell carcinomas in the genitofemoral region where a triangular cicatricial area (irradiation) showed metastases, some of which had been removed by cautery In both inguinal and gluteal regions, on the base of the penis and on the scrotum there were large ulcerations. In the left groin there was deep necrosis, from which an extensive cellulitis extended into the quadriceps muscle of the left thigh. Numerous retracted, subpleural, snowflake-like pulmonary metastases were seen, particularly in the left lung

Skin sections of inguinal ulcerations revealed a deep ulcer with extensive necroses, polymorphonuclear and round cell infiltrates and deep invasion with tumoral tissue. The latter arranged in strands or

(7) Hautarzt 8 213-215, May 1957

bundles, showed small to medium-sized cells with vesicular ovoid nuclei. Occasionally an adenoma like structure was noted. No cellular polymorphism was seen.

Histologic examination of the pulmonary metastases disclosed alveolar sometimes lacelike pattern or festoon like arrangement of tumoral tissue the cellular elements of which showed a small vesicular nucleus with medium chromatin contents.

Histiogenesis and nosologic classification of basaloma are still under discussion. Generally it is assumed that basal cell epitheliomas do not metastasize that however exceptions to this rule occur (Lever). Referring to the present case and others in the literature the author refuting a suggested distinction between basaloma and basal cell carcinoma includes basalomas among the malignant skin tumors because of the locally destructive growth and the possible, though rare formation of metastases.

► [A very unusual case in many respects. The problem of immune responses to malignant tumor tissue is now receiving increasing attention. The patient had multiple large basal cell epitheliomas (not *superficial* basal cell epitheliomas) with extensive metastases. Apparently his natural resistance to the malignant basal cells was extremely low. In a sense this is just the reverse of what is seen in patients with multiple self-healing epitheliomas. The latter apparently have an extremely high degree of immunity to their tumor tissue.—Eds.]

Mycosis Fungoides Case with Unusual Beginning. Enrique E. Tello and Pedro E. Guillot[8] (Córdoba, Argentina) believe that of the three clinical forms of mycosis fungoides, the Alibert Bazin type not only possesses all the clinical and even the histologic characteristics needed for an autonomous entity but that it also lacks any of the characteristics that might justify its inclusion in the bizarre group of the lymphoblastomas. The Vidal Brocq type with initial tumors, is regarded by most authors as being usually a variety of lymphosarcoma in the widest sense of the term although it may occasionally represent either the first manifestation as a cutaneous exteriorization of Hodgkin's disease or a similar condition consisting of an infectious reticuloendotheliosis with tumoral exteriorization. The erythrodermic or Hallopeau Besnier type is regarded by Bluefarb as a manifestation of lymphatic leukemia, Hodgkin's disease or lymphosarcoma.

Although all three forms have points of contact in certain clinical aspects, and although by straining a point they can be linked together as having a presumptive unity of cause it is clearly artificial and false to class them as lymphoblasto-

(8) A. L. ... dermat. 7 15-20 March, 1957

mas, because closer study shows that each has its own clinical and histopathologic peculiarities. As long as exact knowledge of the cause of the lymphoblastomas is lacking, it is wiser to catalogue each of the forms separately though under a common heading and to reserve the term mycosis fungoides, already so established by use, exclusively for the classic Alibert Bazin type. Since the cause of the disease is unknown no constantly effective treatment has been found. Moreover treatment that is effective in one form may be ineffective in the others which further proves the plurality of their origin. Similar variability exists in the manner in which the disease begins, as shown in the case cited.

Man was first believed to have Duhring's disease. His initial symptom was diffuse pruritus, most pronounced on the legs and especially on both feet; at the same time, he noticed that his skin was drier than usual. He was treated for a supposed liver condition for 6 months, during which time disseminated vesicles and papules appeared, chiefly on the face and anterior wall of the right axilla; the itching and dryness increased. He then consulted another physician, who treated him for about 2 years with bismuth and other injections. At first, the skin symptoms disappeared, but later they returned and then he consulted the authors.

Examination showed a polymorphous dermatitis with a predominance of bullae rising above an erythematous base of irregular outline. Itching was extreme and many traumatic excoriations were present besides the erythematous lesions. The tendency to recur and lack of impairment in general condition suggested a diagnosis of dermatitis herpetiformis, a supposition later supported by the disappearance of the lesions under treatment with chlortetracycline. They recurred, however, when the drug was withdrawn. A histopathologic report before the discontinuance of chlortetracycline stated that the histologic picture was compatible with an eosinophilic or Besnier Boeck Schaumann disease. Several other forms of therapy were tried but after a period of slow gradual improvement, the vesicles, itching and erythema recurred. As these symptoms became generalized and intensified, papular and tuberculous lesions, which later became tumoral, appeared. The diagnosis of mycosis fungoides was then made and confirmed by another histologic study. Treatment with an antimitotic drug administered intravenously was tried. Although it was well tolerated, it had no effect on the disease.

► [W has recently seen a patient with Hodgkin's disease who developed patches which one would unhesitatingly diagnose as dermatitis herpetiformis.

Although it is true that no constantly effective treatment has been found for mycosis fungoides, this need not be simply because the cause of the disease is unknown. Certainly there are diseases for which we know the cause but for which there is no known effective treatment and there are also many diseases for which there is no known cause, which can be helped regularly. That a form of treatment is effective in one case of mycosis fungoides

and not in another does not warrant the conclusion that the disease has more than one causative factor The failure of a given disease to respond to the same medication in every instance may be the result of factors other than differences in etiology —Eds.]

Experimental Investigations on Virus Etiology of Mycosis Fungoides are reported by V Aplas[9] (Univ of Erlangen) In two clinically and histologically indisputable cases of mycosis fungoides excision biopsies were taken from nodules a few days old An emulsion was prepared from this material and after adding penicillin it was inoculated onto the chorioallantois of 12 14 day old chicken embryos. Control studies were done with normal tissues as well as sterility tests After incubation of 5-6 days small well-defined, hemispheric, prominent solitary or grouped proliferation foci showed, the tops of which were yellow white and the periphery dull white. Sterility tests from these foci were negative. Passage inoculation from 2 to 3 such foci yielded, after 48 hours exuberant dissemination of isomorph nodules which later enlarged to lentil size. During the 3d passage most of the chicken embryos died probably due to the increased virulence of the agent. Histologic examination of dead embryos showed perivascular myelin depletion and degenerative changes of nerve cells in the brain the liver was enlarged and there were markedly damaged liver cells (probably toxin effects)

Histologic examination of the chorioallantoic foci revealed distinct proliferation mainly of meso- and ectoderm. In the latter the proliferative changes were associated with degenerative alterations of cytoplasm and cell nuclei often suggesting reticulated and ballooning degeneration in herpes zoster lesions. Occasionally cavities were seen surrounded by edematous vacuolated cells. The nuclei were often pressed aside pyknotic, decaying or crumbling In smaller cavities, round or bizarre hyalin corpuscles existed. In the mesoderm, proliferation was more marked and consisted of polymorphic cells the cytoplasm of which was coarsely granular and acidophilic. In the adjacent vessels eosinophilic granulocytes and small basophilic round cells were interspersed among proliferating cells. In some areas the structure had disappeared completely and was substituted by grayish homogeneous or crumbling necrobiotic sub tances with abundant cellular and nuclear detritus. Near the entoderm were

(9) Arch. klin. u. exper Dermat. 204 93-102, 1957

nodules with blood filled, dilated vessels, the wall of which showed partial cell proliferation and partial destruction.

Since changes of this kind in the chorioallantois can be caused by virus infection, the authors believe the cultivated agent is likely a virus which in the 6th passage shows un changed virulence and proliferative capacity and which may be the causative agent of mycosis fungoides.

► [In addition to further work in other cases and other clinical varieties of mycosis fungoides, Koch's postulates would have to be satisfied before this agent, believed to be a virus, could seriously be considered to be the cause of mycosis fungoides

In the absence of such additional evidence, one must think of other ex planations. For example, it has been shown that in lymphomas and leuke mias there is often peculiar susceptibility to secondary infection and para sitic infestation (for example, with deep and superficial fungi, Sarcoptes scabiei var. hominis, etc.) Moreover it is well known that in blood dys crasias and lymphomas there is an associated high incidence of herpes zoster infections. All of this points in the direction of an altered resistance of the diseased tissue of mycosis fungoides and other lymphomas, etc., per mitting organisms not causative of the disease to exist saprophytically —Eds.]

Primary Reticulum Cell Sarcomatosis of Skin. Two Cases involving the skin only are reported by C. E. Sonck (Helsinki)

CASE 1—Woman, 69, in November 1953 had a few small nodules in the right ear which, within a few weeks increased in number and also appeared on the face, back and chest. On hospitalization a month later disseminated, brownish red, prominent, pinhead- to pea-sized nodules showed, some surrounded by a fine red halo. There was no lymphadenopathy the internal organs were normal. The erythrocyte sedimentation rate was 24 mm. and the blood pressure 185/90. Since February 1954, she had increasing fatigue. The nodules enlarged and finally displayed an ulcerated or necrotic, blackish surface (Fig 40) Hormone analysis (from urine) showed gonadotropin 65 units/L., estrogen <50 units/day and 17-ketosteroids 4.7 mg./day The hemogram revealed eosinophilia (5-10%) and an increasing shift to the left of leukocytes with relative lymphopenia. A retrosternal struma was noted. Since March, the patient had had remittent fever of about 100.8 F. I April an ulcerated nodule of the pharyngeal mucosa was noted accompanied by increased loss of strength and painful foul smelling tumors Death followed on May 1 1954

Autopsy revealed numerous cutaneous tumors surrounded by red margin and with central necroses. The tumor tissue was reddish and distinctly separated from the subcutaneous fatty tissue. Two tumors with central depression were found on the left epiglottic edge. No tumor formation was seen in other organs. Further findings were colloid struma, minor atheromatous changes in the major arteries at the base of the brain, in the anterior descendent branch of the left coronary artery and in the aorta descendens, anthracotic lymph nodes in the hilus region and paratracheal connective tissue.

(1) Acta derm.-venereol. 37 129 139 1957

Histologically the tumors showed an atrophic, partly spongiotic epidermis consisting of compact masses of cells which penetrated the entire thickness of the cutis. Collagen fibers within the tumors were either completely absent or existed only as small fragments elastic fibers were missing silver impregnated sections showed a network of argyrophilic fibers. Tumor cells displayed marked polymorphism the nuclei were large (13-15 μ diameter) round, oval or irregular occa ionally gigantic or forming conglomerates, with large nucleoli



Fig 40 (Courtesy of Sonck, C E Acta dermat.-venereol. 37 129-139, 1957)

and more or less rich in chromatin. Besides, there were numerous large clear cells (25 30 μ diameter) the vesicular nuclei of which had a delicate chromatin framework and well-developed, often multiple nucleoli *Nearly everywhere n the tumors, mitoses* were numerous. These tumor cells, which are usually immature reticular cells with an admixture of stem cells, did not show pigment formation. Mucosal tumors revealed analogue histologic changes the bone marrow was hypoplastic and showed mainly mature cells.

Case 2.—Man 57 In January 1955 had a sudden rise in temperature (up to 102 F) which persisted despite therapy with penicill n, chloramphenicol streptomycin and Rimifon Bacteriologic examination w ve. About 3 weeks after onset of fever small nodular

lesions ppeared on the chest and later spread all over the body On hospitalization (February 1955) small, hardly palpable, reddish papulomacules and pea-sized, prominent livid nodules existed, the latter usually showing vesicle, necrosis or blackish crust. Blood pressure was 145/80 and erythrocyte sedimentation rate, 32 mm. The hemogram was normal at first, but later revealed 170,520 thrombocytes and shift to the left of leukocytes. Electrophoresis showed increased globulins, particularly beta globulins. The mucous membranes were free. After rapidly progressing loss of strength, the patient died in February 1957

An attempt to cultivate tumor cells seemed promising at first, but after 10 weeks, cultural growth came to a standstill and finally the cultures died.

Autopsy revealed multiple cutaneous tumors without involvement of internal organs. The histologic changes of lesions corresponded to those in Case 1

Melanotic Whitlow (Subungual Melanoma) Smith H. Gibson, Hamilton Montgomery Lewis B Woolner and Louis A Brunsting[3] reviewed 52 reported cases and analyzed 38 cases seen at Mayo Clinic. Melanotic whitlow probably represents 3-4% of all melanomas. *Patients are older on the average* than patients with other forms of melanoma. In the 90 cases reviewed, there was no significant difference in sex incidence. The lesion commonly involved the upper extremity especially the left thumb two thirds of the lesions involved a thumb or great toe. Although of questionable significance, trauma was related as an associated factor by more than 40% of the patients. The initial lesion was inflammatory in 37% and pigmented in 32% An abnormality in the nail or a tumor contiguous to the plate comprised the other early lesions Only 12.2% of the patients had pain.

Two thirds of the Mayo Clinic patients had had various surgical procedures elsewhere before the correct diagnosis was made. In only half the total cases was the diagnosis made within 2 years of onset. In about one third, obvious metastasis had occurred by the time diagnosis was made. The malignant nature of the condition was known by 17 patients on admission

The surgical approach at Mayo Clinic was not radical. In most patients with obvious metastasis, conservative amputation was done because it was felt that radical procedures would not change the prognosis. Of the 38 patients, 19 died of melanoma, 3 of whom survived longer than 5 years after operation 6 died of other causes 1 has been lost to observa

(3) J Invest. Dermat. 29 119 39 August, 1957

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(3) J Invest. Dermat. 29 79 129 August, 195

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high index of suspicion plus microscopic examination will accurately establish the diagnosis.

► [The authors of this article state that they were stimulated to carry out this study on the pathologic material of Johns Hopkins University by an editorial comment in the 1954-55 YEAR BOOK, page 280, concerning an article by S. William Becker. Becker stated that of 169 specimens on which the clinical diagnosis of melanoma was made by dermatologists, only 72 (43%) were confirmed microscopically. Of 151 specimens on which a diagnosis of melanoma was made microscopically the correct clinical diagnosis was made in 72 (48%). The editorial comment stated "the statistics here presented by Becker must be highly distressing to all interested in the education and training of dermatologists. We hope that these figures do not hold true for the majority of dermatology departments of medical schools in the United States."—Eds.]

Hutchinson's Malignant Lentigo (Dubreuilh's Circumscribed Precancerous Melanosis): Clinical Characteristics, Histopathology and Differential Diagnosis were studied by David Grinspan and Jorge Abulafia (Univ. of Buenos Aires) in 10 patients (7 women) aged 21-76. None had a history of trauma. In 1 there was a familial history with 2 deaths from multiple melanoma. Lesions were localized on the face in 3 and on the conjunctiva, retroauricular region, arm, scapular region, dorsum, gluteal region and thigh, respectively, in the others. Skin spots had antedated the tumor phase by 2-26 years. Melanomas had been present 1 month to 3 years before admission. Two patients complained of slight itching. In 1 there was no tumor; 2 had solitary tumors; the others had multiple melanomas simultaneous or successive. The lentiginous spot was several centimeters in diameter in 8 and 1 cm. or less in the others. The melanomas were usually pea-sized but 1 was several centimeters wide, with a pedicle.

Histologically, the lesions showed thecae in all patients, and in 1 there was pseudoepitheliomatous hyperplasia. Microscopic diagnosis of tumors was melanoepithelioma in all instances. In 1 case, the tumor was amelanotic. In 2, the lesion resembled spinocellular epithelioma. Recurrent melanomas were noted in 3 patients in whom the lesions were not treated and the tumor was merely coagulated. Adenopathy was present in 1 before treatment and in another 1½ years after operation. Others showed no lymph node involvement. Treatment was electrocoagulation in 3 and surgical excision in the others, with removal of lymph glands in 2. No prophylactic lymphadenectomies were performed. All patients

tion and 12 are still living Six of the 12 were operated on less than 5 years ago and 3 are known to have metastasis. Of the 13 patients with metastasis at the time of diagnosis, 12 were dead within 2½ years Absence of discernible metastasis at the time of treatment did not necessarily herald a better prognosis Metastasis developed subsequently in several of this group

Nine patients were apparently well 5 years after treatment. With the exception of absence of metastasis to the regional nodes and consequent lack of nodal dissection, these cases did not differ significantly from the entire clinic group as to age sex, clinical history and course Had these patients undergone nodal dissection that procedure no doubt, would have been given credit for the better outcome.

Study of tissue from 33 of the 38 Mayo Clinic patients disclosed no practical criteria for grading malignancy or predicting outcome in individual cases. Practically all the lesions were invasive and mitotically active.

► [The index of suspicion of the attending physician should be high for lesions of any type affecting a single nail or its adjacent tissues. As pointed out by the authors, one should be on the alert for (1) pigmentation, (2) chronic onychia, paronychia or granular excrescence that fails to respond to treatment, (3) splitting cracking or displacement and (4) any persistent change following trauma.—Eds.]

Malignant Melanoma Review of Clinical and Histologic Diagnoses is presented by Francis H McMullan and Louis F Hubener[3] (Johns Hopkins Univ) Of 115 specimens diagnosed as malignant melanoma clinically 44 (38%) were verified on histologic examination Of 87 specimens diagnosed as malignant melanoma histologically 44 (50%) were so diagnosed clinically Diagnoses of both kinds included a wide variety of neoplastic lesions

Beerman and associates enumerated the following aids to the clinical diagnosis of malignant melanoma increase in pigmentation in a pre-existing mole radial extension or peripheral halo of pigmentation, increase in size of the mole above the surface or radially ulceration of a pre-existing mole, presence of metastatic pigmented lesions location and hemorrhage or serous exudation from the mole. However one or more of these criteria were found in the lesions clinically diagnosed as melanoma and found to be in error histologically It is concluded that malignant melanoma cannot be diagnosed clinically with any degree of accuracy and only a

(3) A.M.A. Arch. Dermat 7 18-619 December 195

even in healthy skin and generate melanomas with a high grade of malignancy

Recognition of malignant lentigo is definitely valuable because it would explain different degrees of malignancy of melanomas, according to their origin. Practically such recognition has great value in prophylaxis of melanoma. Therapy need not be so radical and mutilating as in other malignant melanomas since in most cases the process can be controlled.

► (It appears to us that Hutchinson melanotic freckle has received increasing attention among dermatologists and nondermatologists alike, since the informative article of Klauder and Beerman (A M A Arch. Dermat. 71 2, 1955) Surgeons who have become aware of this entity now often tend to perform simple surgical excisions of these lesions rather than the radical procedures which they formerly used.—Eds.]

Prevalence, Histologic Types and Significance of Palmar and Plantar Nevi. E J V n Scott, R P Re nertson and C B McCall[3] (Nat'l Inst. of Health) examined 735 persons of all ages for n vi of the palms and soles. At least 1 p g mented lesion was found in 26 5%. F equency of pigmented lesions was lowest in childhood, eached a peak n early and middle adult life and decreased in old age. Histologic ex mination of 45 lesions howed that the histologic type of palmar plantar nevus could n t be predicted cl nically An ntradermal component was noted in 18 75% of the lesions excised from person aged 20-34 n 31 6% from person aged 35-49 and in 70% from persons over age 50

If these 735 persons re epresentati e of the general population, prophylactic removal of palmar and plantar pigmented nevi would be an impractical unrealistic measure for pre enting the proportionately few melanomas that could be expected to arise from the many nevi present on the palms and plantar skin Removal of ll nevi f om the palms d soles, f this were physically possible, would not prevent m lanomas that arise without preceding clinically vi ble nev (a found for a large proportion of melanomas)

De lopment of melanoma from the earliest type of ne u the lentigo has not been shown There is also greement that the most mature form of the nevus the pure ntradermal type rarely if ever becomes malignant Instead the j nctional or compound nevus is considered to be the almost n ariable precursor f malignant melanoma. However m lanoma does not ften occur in childhood a d early adult

[3] Cancer 8 343 347 Mar Apr 1957

have survived to the present and there has been no evidence of cutaneous glandular or visceral generalization.

Histologically malignant lentigo in its first stage must be differentiated from other pigmented lesions, e.g. liver spots and pigmented nevi. Characteristic findings are excess of melanin without other epidermal changes. Ordinary lentigo and junctional nevi are prepuberal lesions and do not show extensive growth. They do not fuse with other similar lesions. Differentiation between senile lesions and the initial stage of malignant lentigo localized on the face may be difficult. Malignant lentigo can however be recognized both clinically and histologically in a later stage when the lesion has become verrucous or covers a raised growth.

The authors offer some general conclusions regarding Hutchinson's malignant lentigo. Clinically the lesion begins as a spot appearing after puberty generally in later years and may be situated on any portion of the skin, but with predilection for the face. Its growth is eccentric and extended by appearance of neighboring satellite spots. Irregular brownish pigmentation is characteristic. It evolves slowly and after periods varying to 34 years may give rise to malignant melanomas. Malignancy of these melanomas appears to be slight in facial lesions but they recur easily without metastasizing or invade regional lymph nodes without generalized metastases. Conversely some lesions on the extremities (palms and soles particularly) may produce extremely malignant melanomas with generalized metastases and death even when the lesion has been present 10 years or more. These should be subjected to careful review for they might be junctional nevi which underwent malignant degeneration. Histopathologic study of these lesions has been faulty in that two different lesions have been confused, and both have been called junctional nevi which are abnormal prepuberal lesions displaying benign junctional proliferation destined to generate nevus cells. Malignant lentigo in contrast, is always postpuberal has expansive and regressive growth by zones and histologically presents an atypical malignant junctional proliferation destined to produce melanomas of low malignant degree as a rule. This malignant junctional proliferation may develop into a lesion of nevus cellular origin (lentigo junction nevus mixed cellular nevus)

dermal and compound nevi. After injection of 1% procaine solution intradermally around the nevus, the top of the nevus was sha ed with a sharp scalpel. Care was taken to obtain sufficient tissue for adequate histologic examination. Light electrodesiccation of the base was then done.

Rebiopsy was done on 112 treated sites after 3-9 months. Specimens were removed by punch excision or scalpel, depending on the size of the remaining tissue. Before-and-after biopsy material was carefully compared. Sections were studied for evidence of increased mitotic ac ti ity comparison of junctional elements present, inflammatory changes, pigmentary changes, cell morphology and scar tissue.

Comparat e histologic studies after electrodesiccation showed that 37 intradermal lesions stayed intradermal 34 compound stayed compound 1 junctional tayed junctional 1 lentigo stayed lentigo 14 intradermal became scar 15 compound became intradermal 7 compound became scar 2 junctional became scar and 1 junctional became compound.

In no biopsy either first nor second was there evidence of malignant change, nor of changing or metaplastic cell morphology There was no ev dence of increased mitotic activity Junctional activity when present in rebiopsy specimens, was morphologically similar to that of the first biopsy and usually quantitatively dim nished. Pigmentation of biopsy sites was fairly common. Two types of pigment change occurred. Often there was a surrounding zone of partial de pigmentation and a peripheral zone of hyperpigmentation wh ch was merely a response of the tissue to heat. Less often there was a ecurrence of central pigmentation This merely represented residual pigmented nevus without s gns of increased activity

Scar tissue was an almost con tant finding in rebiopsy specimens and in 25 completed lesions no remaining nevus cells were fou d. Many rebiopsy areas showed chronic inflammatory changes, consisting of small groups of lymphocytes and increased fibrous tissue. Some investigators believe that uch inflammatory eaction may be responsible for constant irritation of nevus cells and stimulation to malignant change However no evidence was found to support this conclusion, and the authors feel that scar tissue may be important in wall ng-off the nevus.

Treatment of nevi by narrow excision or shave biopsy nd electrodesiccation i satisfactory and cosmetically desirable. *It is* unnecessary to excise widely all pigmented lesions. The simple procedure is saf when carried out by adequately

hood—a time when there is greatest preponderance of junctional type nevi Highest incidence is noted in middle and late adulthood when there are fewer pure junctional nevi and more nevi with intradermal components. If the assumption is made that intradermal nevi transitionally develop from junctional nevi as evidence would indicate, then the consideration that melanomas develop from junctional nevi at a time when such nevi undergo transition to intradermal type cannot be avoided The inferred corollary of this may be that the true precursor lesion of melanoma, more specifically defined is the junctional nevus in transition to the intradermal type in which there is interference with this process

► [The figures speak for themselves. With an incidence of 26.5% for pigmented lesions of the palms and soles (0.5 mm. was the minimal diameter of a lesion for recording) and the extremely low incidence of malignant melanoma developing in these areas, we agree with the authors that surgical excision of all pigmented lesions of the palms and soles is impractical and unnecessary In the past it has been our policy to suggest excision of such lesions principally when (1) they were situated in sites where they were liable to be subject to more than ordinary trauma, (2) there was noticeable change in color size configuration and symptomatology and (3) the patient was particularly anxious to have the lesion removed (e.g because of fear based on knowledge of recent fatal malignancy in the family)

In view of these statistics, if pigmented lesions of the palms and soles are to be removed, the best time would be in early adulthood. But even this is likely to be without benefit in preventing development of malignant melanoma because many such lesions occur without preceding clinically visible nevi.—Eds.]

Electrodesiccation of Pigmented Nevi Biopsy Studies Preliminary Report. Robert G Walton, Roderick D Sage and Eugene M Farber[6] (Stanford Univ) present the first clinical study to determine effects of controlled trauma on the histology of benign nevi. The thesis followed is that partially removed nevi which have been reported to show malignant change later may have been treated initially without biopsy and adequate follow up and may have been undergoing malignant change at the time of the first treatment. Thus it is possible that melanomatous activity was due not to trauma from the procedure but to pre-existing malignancy of the lesion

Method.—Initial biopsy was performed on 168 pigmented lesions from 82 patients. The nevi had been present many years and showed no sign of activity In general it was attempted to obtain fairly small, slightly elevated and moderately or lightly pigmented intra

(6) A.M.A. Arch. Dermat. 76 193-199 A ugust, 1957

an elev ted mass. In lentigo maligna, growth often is associ ated with diffuse, ill-defined pigment infiltration into the surrou ding skin this never occurs in melanocytic nevi.

Pigment n lentigo maligna varies considerably in hue and density from time to time and even at the same time in dif ferent parts of the lesion, and often takes on a bluish to slaty color similar to that noted in dermally derived melanocytic nevi (the latter however do not show the other features listed here) In lentigo there may be at times a pearly trans l cency in the border of the lesion or within its ubstance this is rarely noted in melanocytic nevi. Lentigo may show difference in degree of thickness and irregularity in the ur face ften associated with mottled irregularity of pigmen tation the changes are coarser than those observed in ver rucoid and polypoid melanocytic nevi Lentigo may show superficial bleeding inflammation and ulceration Metastat c maligna cy may appear almost from t beginn ng or more commonly may remain in tu (often intraepidermal with pagetoid features) fo many years

About 50% of melanomas that arise on the kin start n m lanocytic nevi that present the pathologic picture of junc tional activity M lanocytic nevi without junctional ctivity do not ordinarily give rise to malignancy Based on a study f th clinicopathologic correlation of over 300 melanocytic nevi f epidermodermal den ation, clin cal evaluation of mel anocytic nevus often can be a useful guid in predicting presence or absence of ju ctional activity

Junctional activity is almost certainly absent in polypoid ped culated d sessile lesion irrespective of age or loca tion nd also in dome-shaped lesions on the head, face and neck fter puberty Juncti nal ctivity is pr bably absent in dome-shaped lesions in any location in the prepuberal pe riod (provided these lesions are not inflammatory or under going rapid growth) and also after puberty when found on the trunk extremit es and anogenital region and in pla n flat lesions in persons ove age 30 except on the hands feet nd anogenital region. Junctional activity probably pres ent n plain flat lesions in the first 3 decades f lif and t all ages when on the hands, feet and anogenital region often present in slightly elevated verrucoid and halo lesion fter puberty and almost certainly is present in flat peckled le sions in ll ag groups and at all sites. In this latter category

trained physicians provided initial treatment is accompanied by competent pathologic evaluation of tissue removed. Objective diagnosis without biopsy is to be condemned. In this study 11 lesions were shown pathologically to have been incorrectly diagnosed clinically. These included 6 seborrheic keratoses, 2 pigmented basal cell carcinomas, 1 intradermal cyst, 1 actinic keratosis and 1 cutaneous tag.

The authors believe that junctional nevi should be excised or completely destroyed only because of malignant potential and not because they found any evidence that electrodesiccation predisposes to malignant degeneration of the treated site. Because of the greater malignant potentiality it is recommended that nevi which show growth, darkening, recent appearance, exudation or ulceration and subjective discomfort be completely excised.

► [The authors plan to carry out follow-up examinations at intervals of 4-6 years. This prolonged follow-up is necessary, as it has been suggested that it takes several years for malignancy to develop after partial removal of pigmented nevi. If all lesions treated in this study can be followed and all remain benign, the results will have to be weighed carefully against incidence of melanoma from untreated lesions in a similar population. Because of this, it will be necessary to simultaneously follow similar but untreated lesions in control patients. In considering this entire problem, it must be remembered that it has been estimated that only 1 of 1,000,000 pigmented nevi becomes a malignant melanoma.

We are not in accord with the belief that all junctional nevi should be excised or completely destroyed because of their malignant potential. This seems not only unnecessary but also impractical. (See also the preceding article.)—Eds.]

Melanocytic (Pigmented) Nevus: Discussion of Its Management. Bertram Shaffer[7] (Univ. of Pennsylvania) suggests the term "melanocytic" nevus as more satisfactory than the designation "pigmented" nevus or common "mole" because the lesion is made up of melanocytes. This name will differentiate it from pigmented spots of other cellular constituents with which it often is confused.

Most melanomas arise from the skin in two ways: *de novo*, beginning in presumably normal skin or as a pigmented spot clinically known as lentigo maligna, or in a melanocytic nevus of junctional derivation with junctional activity. Onset of lentigo maligna is usually after age 50, whereas most melanocytic nevi appear in the first 3 decades and usually before age 20. There is progressive lateral spread of lentigo, usually slow but at times rapid. Lateral growth of melanocytic nevi is exceedingly slow, upward and outward to form

(7) J. Chron. Dis. 6:109-119, August, 1957.

an elevated mass In lentigo mal gna, growth often is associated with diffuse, ill-defined pigment infiltration into the surrounding skin this never occurs in melanocytic nevi

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Junctional activity is almost certainly absent in polypoid, pedunculated and sessile lesions irrespect ve of age or loca tion and also in dome-shaped lesions on the head, face and neck after puberty Junctional activity is probably absent in dome-shaped lesions in any location in the prepuberal period (provided these l sions are not nflammatory or under going rapid growth) and also after puberty when found on th trunk, extremities and anogenital egion and in pla n flat lesions in persons o er age 30 except on the hands, feet nd anogenital region. Junctional activity is probably present i plain flat lesions in the first 3 decades *of life* and at all ages when on the hands, feet and anogenital egion often s present in lightly elevated, verrucoid and halo lesions after puberty and almost certainly is present n flat peckled le ion in all age groups and at all s tes. In thi latter category

belong also slightly elevated, halo and verrucoid lesions in prepuberty and dome-shaped lesions in prepuberty with rapid growth and inflammatory features (often juvenile melanoma)

Only about 1 of about 1 000,000 melanocytic nevi becomes malignant and many patients have 20 or more lesions. In preadolescence when junctional activity is most often present melanoma is rare. Therefore wholesale removal of these lesions often is impractical Melanocytic nevi may be prophylactically removed when they show signs of incipient malignancy such as rapid growth change of color infiltration of pigment into the surrounding tissue ulceration, bleeding inflammation or satellite adenopathy are present on the hands feet and anogenital region are subject to trauma and show signs of having retained junctional activity after age 40

The only way to remove a lesion with clinical signs of junctional activity is by total excision with a reasonably wide border of normal skin and deep enough to reach into the subcutaneous tissue. This must be followed always by biopsy Lesions without clinical signs of junctional activity may be treated for cosmetic reasons In all cases however histologic control is necessary

► [The limits of correct clinical diagnosis of pigmented lesions have been stressed by S. W. Becker, Jr Although Shaffer's classification of melanocytic (pigmented) nevi of the skin cannot be expected to allow for correct clinical diagnosis in every instance it should prove of distinct clinical aid to the practitioner We hold some reservation, however to use of the word "halo because this may well cause confusion among the uninitiated with leukoderma acquisitum centrifugum, also known as "halo nevus. —Ed.]

Abscess Formation in Pigmented Nevi Report of Three Cases is presented by Thomas S Saunders[8] (Univ of Oregon) Each patient suddenly noted induration and tenderness in a mole present for many years In 1 bleeding followed slight trauma The clinical picture without the usual signs of inflammation was suggestive of malignant disease, but microscopic examination revealed abscess formation in [illegible] nd cated

lar infections such as furuncles It is logical to ass[illegible] trauma such as rubbing or plucking damages the hair and it in turn acts as a foreign body

(8) A.M A. Arch. Derm. 76 189 192 A gust, 1957

► [In our experience, the possibility of infection, inflammation and abscess formation in pigmented nevi, especially in hairy ones, must alw ys be kept in mind in order to avoid misdiagnosis and mishandling of such lesions. Often these changes are caused by plucking of the hair.—Eds.]

Neurocutaneous Melanoblastomatosis with Hydrocephalus Communicans is reported by Andreas Fanconi[9] (Univ of Zurich) in 2 boys who died of hydrocephalus communicans internus at age 12 and 5 months. This rare syndrome is characterized by pigmented nevi of the skin cellular proliferations with melanin deposits in the leptomeninges of the brain and spinal cord, spotty cellular melanosis in the cerebral substance, particularly in the brain stem and cerebellum and hydrocephalus internus communicans

Autopsy revealed partly disseminated partly enormous hairy pigmented nevi cellular proliferations in the leptomeninges of the brain and spinal cord, with perivascular penetration into the brain substance and partial melanin formation, and marked accumulation of melanin in the perivascular and glia chromatophores in the cerebellum pons and brain stem In the second infant, a melanoblastoma in the pons was noted.

The cellular proliferations in pigmented nevi, leptomeninges and brain were structurally identical (nevus cells) and genetically equivalent. The modern concept of nevus pigmentosus is that of excessive formation of Schwann cell of cutaneous nerve endings. These cells originate genetically from the neural crest of the young embryo Leptomeninges also are considered to be derived from the neural crest, i.e., the ectoderm. Both formations can differentiate melanoblasts (melanin-producing cells) This occurs to some extent also in normal development In leptomeninges pigmentation is clearly marked on ventral surfaces of the medulla oblongata, cerebellum and brain stem.

The pathologic development of melanoblasts are the same in the skin and leptomeninges. Excessive formation of these cells appears to be the cause of pigmented nevi and leptomeningeal melanosis which may occur alone or combined as neurocutaneous melanoblastosis. Both nevus formations may develop into malignancies. In the skin malignant melanoma may form in the leptomeninges, melanosarcoma. Intracerebral proliferations of nevus cells may be explained as originating from groups of melanoblasts that were detached

(9) Helvet. paediat. acta 11:376-402, October 1956.

from the leptomeninges and displaced into the brain substance

Formation of hydrocephalus internus communicans is connected with dense, mainly perivascular proliferations in the leptomeninges of the brain and spinal cord which seriously interfere with resorption of cerebrospinal fluid.

Neurocutaneous melanoblastomatosis is obviously a congenital systemic ectodermal dysplasia that may be included in the group of neurocutaneous syndromes (phakomatoses) which also comprises neurofibromatosis Recklinghausen, tuberous sclerosis Bourneville and neurocutaneous hemangiomatoses (retinocerebellar angiomatosis Hippel Lindau and encephalotrigeminal angiomatosis Sturge Weber Krabbe) In the syndrome of neurocutaneous melanoblastosis, heredity is possible but not proved

Syndrome of Peutz Jeghers Association of spotty pigmentation of the labial mucosa palms and soles with intestinal polyposis was described by Peutz and later by Jeghers K. Kitamura R. Kojima and S Sasagawa[1] (Univ of Tokyo) review 13 observations from the Japanese literature and add 5 cases

Among the 18 patients pigmentation occurred congenitally in 3 neonatally in 3 at age 2 5 years in 6, during childhood in 2 and at puberty or during adolescence in 2. Pigmentation appears to be more marked with increasing age perhaps due to mechanical stimuli. Familial occurrence of pigmentation was noted in 7 Association of pigmentation with intestinal polyposis occurred in 5 but it must be noted that intestinal polyposis was ascertained (by x ray rectoscopically) in patients with pigmentation and gastrointestinal symptoms, e g diarrhea disturbed passage ileus or intussusception.

Pigmentation was more marked on the upper than on the lower lip and on the volar aspects of fingers and toes than on palms and soles. Occasionally fine pigment macules were noted in the introitus nasi Pigmentation of lips and buccal mucosa was rather dark brown that of palms and soles fingers and toes often greenish black due to the optic effect of accumulation of melanocytes shining through the thick yellowish horny layer (Fig 41)

Histologically pigmentation of labial mucosa showed in

(1) Hautarzt 8 154-159 April, 1957

creased melanin deposits in basal cells and dopa positive mela ocytes between them. P gmentatio of palms and soles revealed agglomerations of melanocytes on the tips of the crista profundae intermedia of the epidermis but scanty dopa-positi e melanocytes on the cristae profundae l mitantes. Melanocytic agglomerations on the cristae profundae intermedia in the palms and soles corresponded to findings



Fig —Numerous large greenish-black macules on soles and flexor aspects of toes, with intermediate areas on soles remaining free. (Courtesy of Kawamura, K et al Hautarzt 8 34 [illegible] April, 1957)

in ola pigmentation the Macacus rhesus Because of these findings and because pigmentations similar to the spotty ones noted in the authors patients were observed on the labial mucosa introitus nasi, palms and soles of chimpanzees, atavistic factors were assumed to be a significant factor in the genesis of pigmentations in th Peutz Jeghers yndrom which nosologically may be included in the group f phakomatoses.

Mesodermic Melanotic Genodysembryoplasias. Under this heading M I Quiroga, E. F llman and P H. Magnin (Buenos Aires) group two dysembryoplasias—the blue nevus and the ophthalmomaxillary nevus fuscocaeruleus and a

3) Ann dermat et syph. 83 501 1 2, Sept -Oct 956

genetic pigmentary affection—the mongolian patch. Using data obtained from clinical and histologic material studied during the last 5 years they define and classify the clinical, histopathologic and nosologic characteristics of these geno-dysembryoplasias

Renewed attention has been given to blue nevi because of the interest aroused in pathologists and dermatologists by nevi in general with the study of their constituent cells, their possible malignant degeneration and their differential diagnosis in relation to other mesodermal pigmentations. Clinically the blue nevus appears as a firm rounded, well-defined hard blue papule or nodule 3-15 mm. in diameter or as a bluish macule with a regular outline, usually 1 3 cm. in size but sometimes larger (17×6 cm in one case) or intermediate between these two extremes.

The nevus may be blue (52%) blackish blue (32%) grayish blue (8%) steel blue (5%) or black (3%) The steel blue and black types sometimes require histopathologic study to distinguish them from malignant melanoma The color of the nevus depends on pigmentation of the epidermis, depth at which the nevus cells are found quantity of melanin they contain and purity and dominant wavelength of the pigment. In general they are single and appear mostly on the distal part of the extremities the face or less often on the trunk.

Histopathologically diagnosis of blue nevus rests on distribution and structure of the nevus cells which are characteristically fusiform and appear by preference around veins, sweat and sebaceous glands nerves hair follicles and muscle fibers. The cells are apparently mesodermal in origin Two special types of blue nevus—Allen s cellular type and his malignant cellular type which was found by him in 4 patients and was accompanied by small lymph node metastases that did not threaten life—were not found in any of the more than 2 000 cases studied In no case did blue nevi show malignant degeneration Such degeneration is rare and most of the cases reported probably represent errors in diagnosis.

The mongolian patch a circumscribed congenital melanosis peculiar to the darker races is characterized by the appearance of clear bluish or blackish round or oval macules 0 5-6 cm in size localized in or near the sacral region In

the rare cases in which it appears elsewhere it is referred to as an aberrant mongolian patch. As a rule the mongolian patch which is extremely rare in white children, disappears by the 4th or 5th year of life.

The ophthalmomaxillary nevus fuscocaeruleus of Ota (Fig 47) regarded by most authors as an aberrant mongolian patch, should be accepted as an independent clinical entity True, the mongolian patch, the aberrant mongolian patch and the ophthalmomaxillary nevus fuscocaeruleus are histopathologically alike the ep dermis and the superficial der-



Fig —Ophthalmomaxillary nevus fuscocaeruleus of Ota (pigmentation of conjunctiva, lower eyelid and orbital region) Courtesy of Quevega, M I et al Arch. dermat. st syph 33 301-312, Sept Oct 1936)

mis are intact, but fusiform cells (a few star-shaped) laden with pigment appear in the middle third of the dermis. These cells, which are less numerous than those found in blue nevi, do not produce a cha ge n the structure of the dermis. Clinically the ophthalmomaxillary nevus fuscocaeruleus is distinguishable from the mongolian patch and the aberrant mongolian patch because (1) whereas the mongolian patch and berrant mongolian patch recede and usually disappear after the first years of life, it persists and sometimes progresses and (2) the typical distribution of the pigment of th ophthalmomaxillary nevus fuscocaeruleus in the sclera, conjunctiva, cornea, eyelids, iris, uvea, face, l ps, buccal mu cosa and leptomeninges sets it apart and gives it a separate individuality

"Lentigo Achromiant" in Albinos. During the last 2 years M Ito J Noguchi and A Komatsu[3] (Sendai) noted 8 cases of complete albinism (about 1/1,000 of the general skin diseases) on their service 3 patients presented amelanotic cellular nevi

Girl, 20 had dull white skin and white hair The irises were pink, and tolerance for light was poor Ophthalmologic examination revealed horizontal nystagmus and myopic astigmatism. On the cheek, a soft, rounded, lentil sized eruption with definite contours and wrinkled surface, projected slightly and was perceptible to the touch (Fig 43) It was a deep pink, whereas the surrounding area was



Fig 43—Eruption on cheek and neck of albino. (Courtesy of Ito, M et al Ann. dermat et syph 83 631-635 Nov Dec 1956.)

ivory Similar eruptions or patches, 27 in all visible on the temple neck trunk and limbs, had been present since childhood.

Histologic study of sections from the lesions on the cheek and thorax showed that the epidermis was thinned and covered with keratotic scales and that its basal layer was completely devoid of pigment. The lesions were characterized by the presence of special cells coming from the epidermis by segregation, cell isolated or in groups as a result of infiltration deep into the papillary and subpapillary dermis. These groups were composed of globular or polyhedral cells separated from one another by a matrix of connective tissue so that the groups were alveolar and variable in size and shape The cells were free from melanin, and it was impossible to obtain any dopa reaction from them.

The lesions were obviously of the same nature as cellular nevi i.e. they were soft nonpigmentary nevi or as the authors propose to call them somewhat paradoxically "lentigo achromiant" Similar eruptions were found in a girl,

(3) Ann dermat et syph 83 631-635 Nov Dec 1956.

aged 11 and a boy aged 8. The other 5 patients, all children under age 4 were free from cellular nevi. Because of the character of these lesions the authors believe that they may appear sooner or later in these patients.

Serochemical studies were done in 5 patients, including the 3 with amelanotic cellular nevi. The levels of tyros ne copper a d oxydase in the blood serum were about normal but the peroxydase reaction in the circulating leukocytes by Sato s method (30 seconds to 2 minutes) was obviously delayed as compared with normal subjects (physiologic le els 3-5 seconds) This delay in reaction seems to be the only abnormal biologic stigma in the pathology of albinism. Tests for phenylpyru ic acid in the urine were made in 4 and results in all were negati e

Storiform Neurofibromas of Skin, Pigmented and Nonpigmented. Amo g some 100,000 biopsies, Blahoslav Bednár[4] (Cha les I\ Univ Prague) observed 9 cases of a peculiar benign skin tumo with a microscopic structure similar to matting The term storif rm (storia matting) was adopted to describe such tumors. A erage duration of the tumors before extirpation was 9 months Growth in all cases was rela t vely low but continuous. S e varied from that of a pea to that of a closed fist. The tumors were freely movable in relation to the subcutaneous tissues but were adherent to the skin. Surgical rem al was s mple the tumor shelling out of the surrounding tissue with ease The trunk appears to be th site f predilection.

Superficially the tumor resembles histiocytoma, xanthofibroma or sclerosing hemangioma but differs from these tumors by absence of hemos derin and udanophilic lipids and by its progressive though rather slow growth. Sometimes, the tumor cells contained melanin suggesting origin from blue nevus, but history of previous pigmentation of the skin was absent in all

Th haracteristic matt ng like structur was found only at the center of the tumor This structure originated i the grouping f elongated, spindle-shaped tumor cells into small egula ly arranged clusters in which nuclei predominate so that the lusters ppeared like little stars or bilateral brushes ccording to the plane at which they were cut through on section. Nuclei of the tumor cells, in a sect on cut through

( ) Cancer 10 348 376, Mar Apr 957

their flat surface appeared widely oval at the center of the stars At the periphery of the cluster the nuclei had undergone rotation of 90 degrees and were noted as narrow deeply staining spindles The high cellularity of the tumor made it resemble fibrosarcoma but mitoses were rare. The lesion apparently has neurogenic origin but differs from the usual neurilemmoma by presence of melanin.

Average follow up after extirpation was 5 years. In 1 patient, the tumor recurred 7 months after removal but there had been no regrowth 3 years after the second operation. No other recurrence was observed

Precancerous Dermatoses and Intraepidermal Cancer of Anal Region According to Lewis Grodsky[5] (Univ of California) such lesions are seldom mentioned in the literature but unquestionably have a bearing on some of the later advanced lethal malignancies of this region. Increasing awareness of these lesions and the possibility of early malignant changes in some of the more common chronic inflammatory conditions would undoubtedly contribute to decrease in the high mortality rate of the later advanced anal malignancies Perhaps like the dermatologist the surgeon should make more frequent use of biopsy study of the bizarre clinical anal lesions noted in leukoplakia Bowen's and Paget's disease and other dermatoses that have malignant portent. A more exacting study of the pathology rather than routine examination is also desirable.

Clinically presence of slightly elevated, marginated grayish white keratinized patches on the anoderm or transitional anal canal mucosa is suggestive of leukoplakia Biopsy is necessary for confirmation and to classify the stage of leukoplakia for proper treatment This lesion is definitely one of the precancerous dermatoses because of its natural evolution when untreated to squamous cell cancer Local excision of the leukoplakic anal lesion should suffice in the precancerous and intraepidermal phases An anoplastic procedure with sliding or pedicle skin grafts sometimes may be necessary for large patches Microscopic evidence of invasion with possible metastases demands radical operative treatment and inguinal gland dissection Irradiation has proved impractical and often ineffectual for leukoplakia in the anal region

(5) Am. J Surg 93:89 94 January 1957

Any mole found in a location subjected to chronic irrita tive trauma should be excised while it is still in the precan cerous state In premalignant pigmented tumor of the anal region, the best treatment is wide and sufficiently deep exci sion followed by careful microscopic examination of the en tire lesion for possible malignant transformation

In Grodsky's opinion cancer is prone to develop in unsound tissues of the anal region that have been weakened by the chronic infection and irritation found n long-standing fistulas lymphopathies cicatrices and similar conditions. In *lew of steadily increasing evidence*, all chronic indurative inflammatory lesions should be excised and examined mi croscopically Malignant anal disease can develop so insidi usly that in ts incipiency it may be difficult to distinguish from benign dermatoses. The fine distinction between an early stage of anal cancer and chronic inflammatory hyper plasia can often be an arbitrary one Therefore when biopsy reveals infl mmatory hyperplasia, careful search hould be made for early neoplasia.

Radiodermatitis shows malignant transformation in a siz able percentage of cases. The change begins as an in situ lesion showing intraepidermal anaplasia not unlike Bowen's epithelioma. Biopsy is always necessary to dentify the changes and to indicate the proper surgical approach.

Th clinical lesion of Bowen's disease is not character istic tself and may mimic benign lesions such as papilloma, condyloma, eczema psoriasis nd others. It eventu ally appears as a crusted, oozing granulomatous area Ex cision biopsy is alway advisable for diagnos s for evalua tion of activity and as gu de to adequate surgical treatment. I the early ntraepidermal stage, wide local excision s sufficient. An anoplastic procedure may be required for more extensive denudation. If the basal cell layer of the epidermis is disrupted and dermal nvasion is noted, radical surgery is necessary

Less than a dozen authenticated cases of Paget's disease in the anal ea have been reported. Clinically the lesion is characterized by spread ng slightly indurated or infil trated inflammatory areas of dusky erythematous skin show ing scaling oozing and crusting This condition may resemble chronic neurodermatitis or eczema, and perianal itching can be pronounced. A diagnostic biopsy should al

ways be taken of any chronic inflammatory lesion of this type in the perianal region If there is evidence of invasion after careful biopsy study wide local excision should be performed. If there is evidence of lymph gland metastases, radical surgery is indicated and prognosis should be guarded.

► [It has become relatively easy to relieve most complaints of pruritus ani with modern therapeutic agents. Some older modalities, such as x-rays, tattooing sitz baths, wet compresses, etc., are less often required today Therefore many cases are no longer seen by the specialist and some are not seen by any physician. However to relieve the symptoms in an area such as this, where the patient is unable to view the local changes, without benefit of proper medical attention is to invite possible serious sequelae —Ed.]

Borst Jadassohn Epithelioma Re-evaluation. The so-called Borst Jadassohn intraepidermal epithelioma is a rare, superficial cutaneous lesion consisting of scaling or verrucous plaques which remain fixed in size or grow slowly over a period of years According to Robert W Goltz Ramon M. Fusaro and Samuel E Sweitzer[6] (Univ of Minnesota) the long duration of these lesions suggests that they may not be carcinomas Invasive tumors in untreated lesions have not been reported except in the somewhat equivocal first case of Jadassohn

Histologically cellular changes limited to the epidermis consist of nests of darkly staining cells resembling basal cells and nearby derangement of squamous cells. These cellular changes have been assumed to represent carcinoma because with ordinary staining the nests of basal cells resemble basal cell carcinoma and the derangement of prickle cells suggests squamous cell carcinoma However the morphologic alterations in the prickle cell layer are comparable to similar changes in certain epithelial nevi seborrheic keratoses and other benign epidermal lesions In accepted preinvasive lesions such as senile keratosis and Bowen s disease, the changes are not primarily those of general derangement of the architecture of the prickle cell layer but a disturbance of single cells

Nevertheless the similarity of the nests of darkly staining cells to basal cell carcinoma cannot be lightly dismissed. The authors know no benign lesions showing these changes. Basal cell epitheliomas rarely if ever contain glycogen, whereas squamous cell carcinomas often do In sections of Borst Jadassohn epithelioma stained by the McManus technic, the darkly staining islands contained no glycogen in

(6) A.M.A. Arch Dermat. 75 117 122, January 1957

dicating that they were actually derived from the basal cell layer

Another interpretation is possible, however It is known that prickle cells commonly give rise to basal cells during epidermal repair following injury Possibly in this condition in which there is active proliferation of unusual nature of the prickle cells some might take on the form and staining characteristics of basal cells, without representing actual basal cell carcinoma. If this hypothesis were true the final result could be explained by abnormal activity of cells of only one layer of the epidermis However the fact that the islands of basophilic cells appear to be continuous with and hence presumably arose from the basal layer of the epidermis weighs agai st this therapy

The authors agree with others that so-called Borst Jadassohn ep thelioma is probably not a combined basosqua mous cell carcinoma. The eosinophilic cell masses do not appear to be malignant and any conclusion that the masses of basophilic ells re basal cell cancer is premature though a ailable hnical and histologic evidence does not permit any definite conclusion.

▸ [The slow growth and long duration of these intraepidermal tumors do not necessarily rule out the diagnosis of carcinoma. As is well known, these same features can be observed in other lesions of undoubtedly carcinomatous nature.—Ed.]

Cytodiagnosis of Cutaneous Malignancy Frederick Urbach, Eugene M Bu ke and Herbert L. Traenkle[7] (Buffalo) examined 500 skin biopsies by a smear method and by rou tine histologic section. In specimens obtained by curet, the base f th biopsy was gently rubbed over the surface of a slide mmediately after removal from the pat ent. Punch bi opsies were cut with a scalpel perpendicularly to the plane of the specimen and the freshly cut surface of one of the hal es was rubbed gently o er a slide Preparations were immediately placed in a glass jar contain ng equal parts of alcohol and ether fixed for a minimum of 20 minutes and then stained accord ng to a modification of the Papanicolaou technic.

The cytologist examining the smears and the pathologist exami ing the histologic sections reported their findings n dependently without being informed of the clinical diagnosis. At completion of the study all smears and sections in

(7) New York J Med. 56 1461-1464, Nov. 15 1956.

which there was any disagreement between cytologist and pathologist were reviewed by the entire study group. Of the 500 biopsies taken 348 were diagnosed as malignant and 152 as benign Among 335 biopsies of malignant lesions, definite cytologic diagnosis was made in 303 Malignancy was recognized but the exact nature of the tumor could not be determined in 32 In 7 the smears were reported as negative when the biopsy sections were clearly positive 6 smears were insufficient for any diagnosis.

The pathologists reported 5 of 335 specimens as insufficient In 7 biopsies diagnosis was changed from negative to positive on review of serial section recuts In 9 biopsy specimens reported as negative rebiopsy clearly showed cancer correctly diagnosed by the original smear

In benign lesions diagnostic accuracy of the routine pathologic section was clearly superior Definite cytologic diagnosis could be made in only 90 of 152 specimens 8 of these were falsely reported as positive for malignancy when recut of the section and clinical diagnosis showed no cancer

The study indicates that accurate specific diagnosis can be made by cytologic study of stained smears obtained from biopsies of cutaneous malignancies Interpretation of such smears however requires considerable experience. Microscopically there are striking differences between smears obtained from malignant and from benign skin lesions. Distinguishing features are found in the appearance of individual cells and in the number and arrangement of the cells adhering to the slides

Although the smear technic is relatively rapid, simple and of a degree of specificity that compares favorably with routine histologic examination its disadvantages lie in the need for training in cytology the impossibility of defining the exact extent of the lesion and the difficulty of specifically diagnosing benign lesions Cytologic examination of cutaneous malignancy is not to be considered a substitute for histologic study but rather should be used as an adjunct pro- ... microscopy

Changes o ... tients with carcinoma Ca and K blood levels are normal

but in the fast-growing tissues of malignant tumors, Ca content is considerably decreased and K content increased. The Ca deficiency of the proliferating tumor cell is accompanied by increase of its permeability which can be determined by measuring the electric conductivity. In studying permeability conditions of various skin disorders by the electrodermatogram EDG N. Melczer and J. Kiss[4] (Univ. of Pécs) observed considerably increased permeability in cutaneous carcinoma on the intact surface of which modern electrometers showed an increased positive charge.

METHOD.—Unpolarized copper-copper sulfate electrodes, which contained KCl gelatin (prepared with 1/10 M KCl solution) were used. Electrodes were connected by siphon tube, the lower end of which was plugged with cotton wool from which filament was pulled out during the test and soaked in N/10 M KCl solution. The negative electrode was placed on the palm, the positive, on the area to be tested. The instrument used was microvoltmeter with d. c. tube and amplifier.

On the basis of more than 1,000 EDG's only values of more than 3 mv were considered to be positive. In various malignancies the following values were found: early malignant changes 4-8 mv; intraepidermal cancer 7-14 mv; early carcinoma with beginning growth into deeper parts 15-25 mv; basal cell and prickle cell cancers 20-40 mv.

In 96 cases of basal cell carcinomas, 14 of spinobasocellular and 26 of spinocellular carcinoma, values were 20-40 mv. In 4 cases of clinically suspected malignancy permeability was normal, and the negative EDG was confirmed by biopsy. Of 45 cases of keratoma senile, 7 were positive with 7-15 mv and showed histologically an intraepidermal spinalioma and 38 showed negative EDG and biopsy. Of 4 cases of erythroplasia, 3 were positive with 7-15 mg. Histologically the negative case (0.5 mv.) showed changes of balanitis plasmocellularis. The EDG values were 7-16 mv in 3 cases of beginning Paget's disease of the nipple and over 20 mv in 6 cases of morbus Bowen. In 2 cases of cancer of the oral cavity the EDG was strongly positive (20 and 23 mv.).

For control purposes, normal skin of patients with senile keratoma (38), verruca senilis (70), fibromata mollia and dura (20), hard and soft nevi (12) and scarry atrophic and hyperkeratotic lesions of chronic lupus erythematosus (6) was used. In all, negative values were obtained (0.5-1 mv.).

Electrometric determinations must be used with caution in eroded or ulcerated areas because electric currents at the

(4) Hautarzt 8:395-397, September 1957

site of injury may change permeability. In such patients, the EDG should be performed at a distance of 2-3 mm. from the edge of the ulceration. Metastases covered by normal, easily polarized skin and malignancies of the connective tissue are not suited for this method which is highly suited for early diagnosis of beginning epithelial malignancies of the skin and adjacent mucous membranes.

► [Very impressive results which warrant continued study and evaluation of this method. It would be remarkable if the diagnosis of epithelial skin tumors could be made *accurately* in vivo without histologic examination, including e.g. reliable differentiation between a senile keratosis which is beginning to undergo malignant degeneration and one which is still benign. —Eds.]

Hidroacanthoma Simplex: Assessment of Selected Group of Intraepidermal Basal Cell Epitheliomas and Their Malignant Homologues. J. L. S. Smith and J. G. Coburn[9] (Univ. of Manchester) emphasize the existence of sudoriferous metaplasia in a number of superficial neoplasms of the skin. The neoplastic cells arise by adnexal deviation of the rete cells. The matrices which they form represent neoplastic primordia in which, under suitable conditions, differentiation into sweat glandular structures will occur. The structure of individual tumors is linked to the degree of adnexal deviation. Six structural variants are recognized, 2 benign and 4 malignant.

Benign hidroacanthoma simplex corresponds to many lesions of the Jadassohn type together with some close relatives in which the multifocal structure is less emphasized. The neoplasms usually form plaques and may be either verrucose or plane. In the verrucose forms, the line of junction of the stratum corneum and the cellular rete is markedly sinuous, though the tumors have an over-all flatness. The verrucosity is due to a nonspecific overgrowth of the epidermis and the tumor matrices lie in an acanthotic rete as discrete and circumscribed nests of cells.

Benign hidroacanthoma simplex also includes certain lesions indistinguishable clinically from seborrheic warts. In these the adnexal deviation is minimal. However, not all tumors correspond to one or the other extreme of structural pattern; some are of an intermediate composition. The fundamental fact about the group of acanthomas is the presence of a sudoriferous metaplasia. The authors feel that this must form the basis of their classification and not speculation as

(9) Brit. J. Dermat. 68: 400-418, December, 1956.

to whether the component elements are of basal or squamous type or both. The matrices constitute neoplastic primordia capable of unidirectional adnexal differentiation. The term "hidroacanthoma simplex" therefore provides a more precise and natural designation than the existing nomenclature.

Malignant hidroacanthoma simplex is a rare neoplasm of the *trunk and extremities*. Like its benign counterparts it is less common on the face, hands and feet. As a rule it shows the slow growth and limited invasiveness of other epitheliomas in these regions. It is divided into invasive and in situ cancers. In two examples of invasive cancer the structural patterns of benign hidroacanthoma simplex are clearly manifest in the noninvasive portions of the rete. Only the number of mitoses and moderate increase of pleomorphism seen in some areas indicate the cancerous trend. Hence the tumors are regarded as consecutive cancers.

Most in situ cancers are probably malignant from the outset or from an early stage and are considered primary cancers. Primary cancers of the adnexal series typify Bowen's disease but only a proportion of the tumors diagnosed as Bowen's disease belong to the hidroacanthoma simplex group. The prolonged in situ course of the primary cancers probably depends on the slow production of immature matrix cells. Production is balanced by maturation rate so that a simplified stratified epithelium results with a surface layer of parakeratotic cells.

Malignant Change Following Herpes Simplex. R. Wyburn-Mason (London) reports squamous cell carcinoma occurring at *sites of herpes simplex on the lips* of 4 men and 2 women, aged 60-70. In 3 patients, the initial lesion almost healed, then broke down and ulcerated. In the other 3 recurrent attacks of herpes simplex occurred. Two of the recurrences followed exposure to sunlight. Malignant change after herpes simplex may simply be an example of what may occur especially in elderly persons, at the site of any chronic irritation or inflammation, and may not be the specific result of virus infection. On the other hand, if all particularly recurrent, cases are due to local infection with herpes simplex virus and since the patients may show abnormal sensitivity to sunlight it may be that infection by the *virus*, which is widespread, is an important cause of malignant

1) Brit. M. J. 2:4 [illegible] 6, Sept. 4, 1957

change. Since the buccal mucosa and the skin of the genitalia and other tissues may also be infected by herpes simplex, there is possibility in some cases that in these tissues too, the infection may be related to the later appearance of malignancy

► [In view of the possibility that the malignant lesions could have preceded the herpes infections we feel that it would be preferable to speak of malignant change *associated* with herpes simplex.—Eds.]

Bowen's Disease after Tick Bite is reported by H. Stauffer (Aarau Switzerland) and W Lutz[2] (Basel)

Man, 69 first had a papule at the site of a tick bite. From the papule a sharply delineated ring-shaped lesion slowly proceeded toward the periphery Clinically though not verified histologically it presented the appearance of psoriasis. After irritation with ammoniated mercury ointment, exudation and scaling occurred. Histologic studies of the lesion, about 1½ years after the bite, revealed an unusual vacuolation of the epidermal cells. Subsequent studies showed Bowen's disease.

After a tick bite atypical epithelial proliferations, even simulating early carcinoma have been observed but Bowen's disease as a sequel of a tick bite has not been described The mechanism by which the tick bite led to Bowen's disease is unknown The extensive and widespread vacuolation of the epidermal cells in the papillomatous part of the first biopsy specimen obscured the appearance of the cellular changes characteristic of Bowen's disease and in some areas simulated the picture of epidermodysplasia verruciformis. This early vacuolization in Bowen's disease has been noted previously

► [The chronological course of events, i.e. tick bite and 1½ years later Bowen's disease, suggests causal relation. However this is a most unusual sequence of events.—Eds.]

Morphea Like Epithelioma Further Observations are presented by J B Howell (Southwestern Med. School) and Marcus R. Caro[3] (Univ of Illinois) Diagnosis of morphea like epithelioma has different connotations to American and European dermatologists This designation should represent only the true morphea like epithelioma as first described by Crocker and Pernet This tumor differs in clinical and histopathologic features behavior and response to treatment from the superficial cicatrizing basal cell carcinoma that most American dermatologists have called morphea like epithelioma Epitheliomas that have a large component of scar secondary to treatment infection injury or some cicatrizing

(2) Dermatologica 115:656-661 October 1957
(3) A.M.A. Arch. Dermat 75:517-524 April, 1957

disease should be excluded from this category with the scirrhous carcinomas of skin due to lymphatic cutaneous extension

Clinical features of importance are striking resemblance to morphea selective localization to the head and neck region yellowish white color absence of rolled edge, pearly border or threadlike elevation at the periphery frequent delling of the surface sclerous consistency infrequent ulceration generally associated telangiectasia on its smooth shiny surface and slow growth. The natural course of the tumor varies from that of a slowly growing lesion in most patients, to an invasive, destructive and very dangerous cancer in others. Metastases have not been recorded.

Histopathologic features are unique and of great value in establishing diagnosis. The epidermis is flattened, with absence of rete pegs. The cancer cells occur in linear bands and nests varying in thickness from 2 cells to wide strands. In most of these the basal type cells are densely packed but in others, they are loosely aggregated. The bands usually are perpendicular to the surface but may be horizontal. Immediately beneath the epidermis is a narrow band of loose corium containing many dilated thin-walled blood vessels. Beneath this lies a wide horizontal band of senile elastosis. The rest of the corium is filled by densely packed connective tissue containing thickened collagen fibers and many elastic fibers. These fibers are especially thickened and whorled concentrically about the nests of cancer cells.

Excision of the tumor is often the treatment of choice, but much wider and deeper removal than usual is indicated. Low intensity radium needle implantation also has proved effective. The chemosurgical procedure introduced by Mohs should also be successful in removing all traces of the cancer*

* [We agree wholeheartedly with the conclusion that x-radiation is not indicated in this type of epithelioma and that total surgical excision of morphea-like epithelioma is necessary for successful therapy. We have not had any personal experience with radium needle implantation.—Eds.]

Hyaluronic Acid in Circumscribed Myxedema and in Stroma of Cutaneous Epitheliomas was studied by J Lengyel and B Vértes (Univ of Budapest)

Man aged 48, showed circumscribed myxedema, consisting of recent, pale, soft nodules and hard, hard, fibromatous nodules and atrophic areas, on the limbs and in the gluteal re-

( ) Dermatologica 113:215-221, October 1956.

gion Cresyl violet staining revealed metachromatic changes indicating the presence of acid mucopolysaccharides, hyaluronic acid and chondroitin sulfuric acid B which can be differentiated from each other because cutaneous chrondroitin sulfuric acid B is resistant to hyaluronidase. Hyaluronidase activity was tested in histologic sections and in vivo.

Two different hyaluronidase preparations were used, one from bovine testes and the other from bacteria. The former dissolved in 1 ml saline contained 150 turbidity units, the latter 100 spreading units To paraffin sections from which paraffin was removed 1 drop of each of these solutions was applied. Sections were kept in a moist chamber at room temperature for 18 hours washed and stained with cresyl violet. It was noted that due to hyaluronidase activity intercellular metachromasia had disappeared but mast cell granules were unchanged

When a few drops of hyaluronidase were injected into a soft nodule the lesion disappeared completely within 1? hours. In a nodule excised 2 hours after injection no metachromasia could be seen Hyaluronidase was repeatedly injected into another soft nodule for 4 days. Massive infiltration with numerous mast cells occurred metachromasia was absent

Thus in vivo and in vitro histochemical examinations ascertained that the metachromatic substance in cutaneous lesions of circumscribed myxedema was hyaluronic acid.

Experiments on hyaluronic acid were also done in 34 cases of cutaneous epitheliomas (22 basal cell and 12 spinal cell carcinomas) by the same method It was noted that hyaluronic acid was present in large amounts in basocellular epitheliomas but was hardly present in the spinocellular type In intraepithelial epitheliomas (Bowen s disease Paget s disease) results varied It appeared that in the preinvasive stage of these types equilibrium between hyaluronidase and hyaluronic acid remains intact for some time, changing later at a certain degree of "cellular unrest "

It is concluded that hyaluronic acid is an important factor in the stroma defense Increased hyaluronic acid around cellular strands in basalomas tends to localize tumoral growth whereas small amounts around spinocellular cell masses permit unlimited growth and formation of metastases.

Keratoacanthoma of Lower Lip Red Margin. Keratoacanthoma is a benign self healing tumor of the skin that grows rap dly for 6 weeks or more, reaches a maximum of 1 3 cm. in diameter and then slowly regresses, leaving a flat atrophic area with crinkled slightly hypertrophic edge While growing keratoacanthoma resembles a well-differentiated squamous cell carcinoma clinically and histologically It occurs



Fig 44 (top) —Lip lesion at [illegible] weeks.
Fig 44 (center) —Lesion at 1[illegible] weeks.
Fig 44 (bottom) —Lesion at 19 weeks
(Courtesy of Wharton, C H and Davis, R A Lancet 1020 May 18, 1957)

almost exclusively on parts of the body exposed to light and is especially apt to occur in outdoor workers particularly those with light skins and fair hair Of 181 lesions reported in the British literature none started on the lip C. Howard Whittle and Roy A Davis[5] (United Cambridge Hosps.) present a case

Farm worker 48, sandy haired and ruddy had keratoses on the face and backs of the hands At the site of a "cold sore" on the lower lip a button like tumor appeared and grew rapidly After 6 weeks, the lesion was 1 cm. in diameter with a large central keratotic plug (Fig 44) Four weeks later it had flattened and the center plug had been shed leaving a granulomatous crater (Fig 45) At 19 weeks after onset the lesion had flattened the crater had healed and the infiltration had almost disappeared (Fig 46) Biopsy at 6 weeks showed an appearance consistent with a diagnosis of keratoacanthoma

► [A variety of tumor that should always be kept in mind when considering the differential diagnosis of prickle cell epithelioma. In doing so, unnecessary extensive surgery might be avoided in some cases.—Ed]

Hyperkeratoses of Hands of Flax Workers Carcinoma of the lower lip of women was observed oftener in Croatia than in other countries the higher incidence being attributed to a peculiar way of spinning in which flax threads were moistened between the lips On one woman worker hyperkeratoses of the lower lip also were seen Implantation of flax fibers in white mice as previously reported produces malignancies (carcinomas, sarcomas leukemias) The same changes could be produced with cigaret paper which is made with flax fibers In workers employed in the rope making industry and handling flax and hemp fibers, hyperkeratoses and carcinomas were observed

Juraj Korbler Ivano Frank and Jelena Nikolic[6] (Zagreb) examined 11 males aged 16-33 and 10 females aged 17-54 who had worked with flax for 1-5 years In all females and in 8 males marked hyperkeratoses were seen on the dorsum of the hands near the distal end of the metacarpal bones chiefly involving the index finger and the thumb and corresponding to contact areas where flax fibers were pulled through Biopsy of one of the most definite hyperkeratoses revealed an epidermal strand penetrating deep into the corium In the end of the strand the cylindric arrangement of basal cells was missing and in two places of the same strand there were pearl formation One female and 3 males from

(5) Lancet 1 101 1020, May 18 1957
(6) Oncologia 9 425-429 1956

the same factory who were engaged in packing and transporting the flax fibers and flax dust showed the same type of hyperkeratosis.

Hyperkeratoses in the hands and lips of flax workers are considered to be precancerous lesions, which because of their occurrence in comparatively young persons and the relatively short exposure period, have not yet become cancerous.

► [The authors also refer to work by Smiley (Brit. J. Indust. Med. 8 265, 1951) in which formation of hyperkeratoses and carcinomas was described on the hands of workers in the rope industry. Exposure to hemp and flax was entailed in these cases.—Eds.]

Fibromas and Pseudosarcomas of Skin were studied by Jean de Brux and Roger Godechot (Paris) Lesions removed from 20 patients included benign localized fibroconnective tissue tumors (15) and ill-defined pseudosarcomatous fibroblastic tumors (5) In addition to routine staining, periodic acid-Schiff (PAS) reticulin iron (Turnbull method) and sudan IV staining were done Benign localized fibroconnective tumors include clinically different and complex tumors, the two extremes of which are dermatofibroma and histiocytoma. Dermatofibroma (denticular dermatofibroma, noduli cutanei, nodular subepidermal fibrosis, tablet-like fibroma [Civatte]) has little cellular content, but contains mainly thick entangled collagen fibers. Histiocytoma is remarkably rich in cellular elements.

Histogenetically benign localized fibroconnective tissue tumors result from minimal, mechanical or slightly infectious trauma (folliculitis?) to a part of the skin favorable to this special sort of reaction partial or total aseptic necrosis of collagen fibers follows with appearance of cells capable of macrophagocytic action on the debris and induces tissue reconstruction which occurs without organization but merely by sclerosing change of the depolymerized basal substance. In angiomatous types sclerosis also results from organization of fibrinous thrombi on vessel walls. Reticulin fibers which form gradually during the reconstructive phase are a complex, intermediary precollagenous lipoglycoproteinic substance with transitory argyrophylia and transformation to sclerosing fibers and masses. In the zones of destruction PAS is strongly positive often coexisting with reticulin and gradually disappearing during reconstruction. The entire

71) Presse méd 64 937 1940 Nov 21 1956

process may be compared to a healing fracture similar to the reconstruction phenomena in keloids desmoids of the abdominal wall cicatricial and postradiation fibromatous and Dupuytren s contracture

Recurrent progressive dermatofibrosarcoma (dermatofibrosarcoma protuberans) behaves as a tumor invading with a true stroma and a tendency to recur if not totally removed. The stroma consists of active hyperplastic fibroblasts surrounded by a fine reticulin membrane of the same thickness throughout. The PAS is negative or weakly positive with the metachromasia absent These fibroblasts are often mitotic voluminous and filled with fine acidophilic Hotchkiss-positive granules Histochemical study of the stroma particularly of reticulin and PAS substance is not only of diagnostic but also of prognostic significance deposits of PAS-positive material between cells and loss of argyrophylia of reticulin fibers may indicate an attenuated malignant character

Whether the two types of reticulin the one transforming into sclerosing tissue (in histiofibroma) and the other seen in pseudo- and real sarcomatous tumors are identical could not be decided by histochemical studies. It appears however that the latter type may play an important part in the extension of the tumors into surrounding tissues Further immunobiologic investigation may reveal whether antigenic substances are possibly connected with the formation of one type or the other

► [The importance of totally excising dermafibrosarcoma protuberans can not be overstressed. Once this diagnosis has been established by biopsy the tumor should be surgically excised with wide margins and deep (to the underlying fascia) if recurrences are to be prevented.

It would be a worthwhile advance, indeed if tissue histochemical changes *could be relied on* to indicate the tendency to benignancy or to malignancy of a particular tissue as suggested by the authors.

In some cases the histologic picture of these fibromatous lesions may be further complicated by the appearance of xanthoma like cells.—Eds.]

Is Lymphadenosis Benigna Cutis a Transferable Infectious Disease? Lymphadenosis benigna cutis which according to Bafverstedt, includes Spiegler Fendt sarcoids and lymphocytoma has been observed with or even transforming into acrodermatitis chronica atrophicans and erythema chronicum migrans The infectious etiology of acrodermatitis atrophicans has been revealed by recent inoculation experiments and seems most probable in erythema chronicum

migrans The first experimental evidence of the infectious etiology of lymphadenosis benigna cutis and new viewpoints on the course histology and therapy are presented by J M Paschoud (Univ of Bern)

In each of 3 cases of clinically certain histologically veri fied lymphadenosis benigna cutis of the earlobe, 30-50-mg particles were excised and homogenized in sterile saline solution or Tyrode solution (pH 7 4) Microscopic and dark field examination of native and stained homogenates, serologic testing (lues, toxoplasmosis leptospira) culture on various mediums and subcutaneous and intratesticular inoculation into rabbits were completely negative

In experiments 1 and 4 from clinically typical, histologically erified lymphadenosis benigna cutis of the right ear lobe of a boy aged 12, small particles of about 30 mg were removed and homogenized in 1.5 cc. Tyrode solution. Then 0 5 cc. of this uncentrifuged homogenate was injected into the ea lobe of test persons 1 a boy aged 12 and 4 a woman aged 26

After a transitory fo eign body reaction (protein?) a clinically typical lymphocytoma developed in the site of the in jection of test person 1 within 6 weeks. Histologically it was the d ffuse type of lymphadenosis benigna cutis with no re action centers (germ centers) and numerous reticular elements in groups of 3-6 cells, with several giant cells and scanty mitoses abundant lymphocytes and plasma cells. Despite 2 treatments of 300 r each contact irradiation the lesion enlarged. It reached its peak about 10 weeks after im plantation and showed beginning involution after 13 weeks despite the fact that by now a total of 900 r had been applied. Twenty weeks after mplantation (10 weeks after first irra diation) olution was clearly evident, and 9 months after implantation heali g was complete.

Similarly in test person 4 after a transitory foreign body reaction a clinically certain lymphocytoma de eloped within 6½ weeks It was still enlarging 9¼ weeks after implanta tion reached maximal de elopment after 10 weeks and then emained stationary because no therapy had been given. The fi st histologic xamination (9¼ weeks after implantation) revealed typical, partly diffuse, partly circumscribed lym phadenosis benigna cutis with reaction centers beginning to

( ) Dermat 1 197 211 May 1957

form numerous grouped reticular elements with giant cells, macrophages some mitoses abundant lymphocytes and numerous plasma cells A second histologic check up 26 weeks after implantation showed more circumscribed lymphadenosis benign cutis with distinct centers large amounts of conglomerated reticular cells scanty mitoses a few macrophages and numerous lymphocytes

In experiments 2 and 3 0 5 cc. homogenate from transmitted lymphadenosis benigna cutis (of test person 1) was implanted into the right ear lobe of test persons 3 a man aged 76 and 4 a man aged 60 The transmitted lymphadenosis benigna cutis lasted for 6 weeks. In both test persons, clinically abortive lymphocytomas formed which after 7 weeks, histologically showed comparatively less marked but typical changes without formation of reaction centers only scanty reticular elements in groups of 3-4 cells numerous lymphocytes and plasma cells Spontaneous complete involution occurred within 10-12 weeks

In experiments 5 and 6 homogenates from artificially transmitted 9½ week-old lymphadenosis benigna cutis (of test person 4) were implanted into the right ear lobe of test persons 5 a man aged 74 and 6, a man aged 26. In test person 5 a clinically typical lymphocytoma formed within 6 weeks. Histologically it was a more circumscribed type with beginning formation of reaction centers numerous reticular cells in clusters few giant cells and macrophages scanty mitoses numerous lymphocytes lymphoid and plasma cells and rare eosinophils The implanted lesion remained stationary for 6 weeks and disappeared without treatment within another 10 weeks Similarly in test person 6 a clinically certain lymphocytoma with marked regional lymphadenitis developed. It showed a distinct healing tendency and 26 weeks after implantation had disappeared without any therapy

As to the causative agent a microscopically visible culturable germ could be excluded It is therefore assumed that lymphadenosis benigna cutis is caused by an inframicroscopic virus not culturable in inanimate mediums It grows very slowly in the tissues involved probably because comparatively small numbers of the intracellular virus elements are freed during the process of homogenization

► [The results of these investigations are difficult to explain, except on the basis of a transferable infectious agent, assuming that control experi

ments are negative with material from "normal" ear lobes and from ear lobes of patients with various types of cellular infiltrates other than lymphadenosis benigna cutis.—Eds.)

Lymphangioma-like Tumors in Kaposi's Sarcoma. Although many textbooks and general reviews mention that lymphangioma like tumors may occur in Kaposi's sarcoma there have been few specific reports in the literature. Francesco Ronchese and Arthur B. Kern[9] (Providence R. I.) report 2 cases.

CASE 1.—Man, 68, born in Italy had many bluish red nodules and

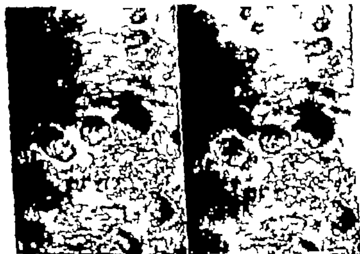


Fig. 47.—Lymphangiomatous tumors. Arrow at right shows one flattened by finger pressure. (Courtesy of Ronchese, F. and Kern, A. B.: A.M.A. Arch. Dermat. 75: 3-427, March, 1957.)

plaques over the lower extremities, with a few lesions on the upper extremities. Both legs were edematous. Biopsy of nodule on the forearm showed Kaposi's sarcoma. On the lateral aspect of the right ankle some of the nodules, which had a gross appearance similar to those elsewhere, could be compressed with apparent deep expulsion of some fluid (Fig. 47). With release of pressure, a depression remained. This was followed by rapid refilling with fluid and return of the previous appearance. Clear fluid with protein content of 3.3 Gm./100 cc. was aspirated from one cystlike tumor. On one occasion after accidental opening of one of these tumors, there was drainage of clear fluid for several days. X-ray study after injection of dye into the cystic tumors showed pooling of the dye in the deeper tissues. Biopsy of one tumor showed lymphangioma.

[9] A.M.A. Arch. Dermat. 75: 1, 17, March, 1957.

The histologist believed that the sections showed lymphangiectasia with proliferation of lymph vessels secondary to obstruction of lymph flow by Kaposi's sarcoma.

CASE 2.—Man, 65 Jewish born in Russia, had Kaposi's sarcoma in the usual locations. Lymphangioma-like tumors were present that could be temporarily emptied by finger pressure.

The authors believe that lymphangiectatic tumors result from lymphatic obstruction by the neoplasm rather than liquefaction of a nodule. Protein content of the fluid removed by aspiration would be consistent with lymph stasis due to mechanical obstruction Serial x ray study after dye injection into the lymphangioma like tumors failed to show rise of the dye, which also would indicate lymph stasis due to mechanical obstruction

Extracutaneous Manifestations of Kaposi's Sarcoma Systemic Lymphoblastoma. Ervin Epstein[2] (Highland Alameda County Hosp Oakland Calif) reports 7 cases and reviews 28 published reports In 23 of the 35 patients the gastrointestinal tract was involved. The liver was affected in 11 the spleen in 4 and the lymph nodes in 8. There was involvement of the genitourinary tract in 7 the respiratory tract in 8, the bones in 6 the heart in 5 and the pancreas, thyroid and adrenals in 2 each In many cases the visceral involvement caused no symptoms or only moderate difficulty Serious symptom occurred only when the heart lungs or gastrointestinal tract were affected Diagnosis of extracutaneous Kaposi's sarcoma must be made by x ray plus the observation of cutaneous lesions or by histopathologic study of surgical or autopsy specimens Visceral involvement occurs in about 10% of cases of Kaposi's sarcoma.

Clinical and histologic association of Kaposi's sarcoma and the lymphoblastomas is much more frequent than would be anticipated from the rarity of these conditions Therefore, it seems possible that Kaposi's sarcoma may be a low grade lymphoblastoma. This concept is strengthened by the occasional seeming mutation of Kaposi's sarcoma into a lymphoblastoma The associated reticuloendothelial hyperplasia in Kaposi's sarcoma is another link in the evidence of this relation

► [We also have seen several cases of Kaposi sarcoma with e tracutaneous manifestations and we share the opi ion that t least in some cases Kaposi's sarcoma is a systemic disease I uch cases, particularly a trial

(2) California Med. 87-98-103 August, 1937

with systemic treatment appears indicated, e.g., with penicillin (Flerini, L. E. and Grinspan, D. Rev argent. dermatosif 32:3, 1948) or with corticosteroids or ACTH (Sulzberger, M. B. and Witten, V. H. A.M.A. Arch Dermat. 73:402, 1956) —Eds.]

Strawberry Hemangiomas: Natural History of Untreated Lesion was studied by Alvin H. Jacobs[1] (Stanford Univ.). Strawberry nevi (cavernous hemangiomas) first appear at or soon after birth as sharply delineated pale areas which become bright red, raised and tense within the first few weeks. A firm subcutaneous mass often develops under the surface lesion and can be felt extending out beyond the area visibly involved. Growth usually rapid during the first 3-6 months of life then slows and early signs of involution appear between age 6 months and 1 year. This spontaneous regression i first marked by decreased tension and color in the lesion. Frequently small spots of blue discoloration appear. They enlarge and coalesce during the second year but soon these fade, leaving islands of normal-appearing skin. By age 5 most of the dull remnants of angioma have disappeared, leaving only more or less atrophic skin which gradually reverts to normal texture.

Review of the literature on the natural history of strawberry hemangiomas revealed overwhelming evidence of the satisfactory spontaneous involution of over 95% of lesions without the scarring and danger of other sequelae inherent in the various forms of treatment. In a study of 105 strawberry nevi observed for over 1 yea Jacobs found that 97% of th lesions had completely disappeared or were regressing satisfactorily. Only 4 lesions failed to show signs of involution and these were small lesions which were present at birth and did not grow d sproportionately during the first month of l f

A cross-section study of 1,735 children examined in pediatric practice showed hemangiomas to be present in 10.1% of all infants from birth to age 1. The incidence dropped to 2.9% in children aged 3 to 5 and to 1.5% in children over 5 confirming th fact of spontaneous involution.

[In addition to his own experience, the author quotes numerous other observers with similar results. We agree with those who practice watchful waiting in managing most strawberry and cavernous hemangiomas. Exceptions to this rule are prompted by (1) extremely rapid growth of the lesion and (2) encroachment and obliteration of such structures as the eye, mouth, nostrils, urethra or anus. In these instances we favor the smallest dose of radiation calculated to reverse the growth of the nevus and start it

(1) California Med. 86:8-10, January 1957

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(2) California Med 47:98-103 August, 1937

Examination of 583 patients and 696 recruits revealed that 34.5% of all aged 20 and 40.15% of all aged 21 had senile angioma. Thus, the designation senile angioma appears to be inadequate.

► [While we have not done a careful study of the incidence of senile angiomas in different age groups, we have seen such lesions in far less than 34.5% of our 20- and 21 year old patients.—Eds.]

Warty Dyskeratoma. Benign Cutaneous Tumor Resembling Darier's Disease Microscopically. Frederick J. Szymanski[3] (Univ. of Illinois) reports 7 cases. The tumor was single in 6 patients, whereas the other had 3 tumors. 3 lesions were located on the scalp, 3 on the right cheek, 1 on the left cheek, 1 on the subtemporal area and 1 under the left breast.

Warty dyskeratoma usually occurs in elderly persons. The clinical appearance is not distinctive. In the present group, clinical diagnoses of verruca vulgaris, senile sebaceous adenoma, seborrheic keratosis, comedone, senile keratosis and epithelioma were suggested before surgical removal. The histopathologic pattern is characteristic and diagnostic, resembling Darier's disease except for the localization of the epidermal tumorous proliferation in warty dyskeratoma. The lesions show a circumscribed epidermal tumor characterized by plugging, papillomatosis, a lacuna-like cleft in the epidermis, corps ronds and grains. Despite microscopic similarities, warty dyskeratoma is apparently not related to, nor does it predispose to, keratosis follicularis.

On first glance, warty dyskeratoma microscopically resembles nevus syringadenomatosus papilliferus, but in the latter disorder corps ronds and grains are absent. Large cysts and villi are lined by a double row of cells, whereas in warty dyskeratoma the villus-like projections are covered by a single layer of cells. The villi in the sweat-gland tumor contain a heavy infiltrate consisting mostly of plasma cells. The villi of the dyskeratotic tumor contain only a few histiocytes. A granular cell layer is completely absent in nevus syringadenomatosus papilliferus. In warty dyskeratoma, the granular layer is missing over a small area just beneath the base of the horny plug, but marked hyperplasia of the granular cells is visible along the sides of the plug. Glycogen is absent in warty dyskeratoma and markedly increased in the sweat gland tumor. In contrast, sections from Darier's disease and warty dyskeratoma react alike histochemically.

(3) A.M.A. Arch. Dermat. 75:567-572, April, 1957.

on a course of slow resolution. We strongly urge that only suberythema doses of ionizing radiation be given and that the time and number of subsequent treatments be based on the *response of the particular lesion to the* preceding irradiation. The lesion itself does not always present the greatest problem of management—often it is the parents or grandparents who feel that something should be done and are not satisfied with watchful waiting.—Eds.]

Clinical and Histologic Features of Senile Angioma are reported by Robert Keller[4] (Univ of Zurich) Histologically 28 cases of so-called senile angioma revealed three different phases of development In the early evolutionary stage senile angioma is a lobulated vascular tumor with unmistakable signs of vascular proliferation and capillary budding which according to Virchow is characteristic of angioblastoma Growth ends comparatively soon In marked contrast with planotuberous angiomas senile angioma is limited to the subpapillary layer

The second phase is characterized by marked dilatation of fully differentiated capillaries. No further papillary growth exists in this phase in which collagen strands around teleangiectic capillaries show beginning degenerative changes. Interjacent elastic fibers are basophilic (elacin)

The third phase is a terminal stage with secondary and degenerative changes The former consists of gradually *increasing vascular dilatation and development of cavernoma* like formations The latter is represented by formation of collacin and elacin which are the result not the cause of vascular dilatation

Corresponding to the three histologic phases are three clinically and morphologically distinct stages. In the fleabite-like initial stage small slightly raised spots suddenly appear often without being noted. The intermediary (grain-of pepper like) stage is most frequently seen and shows round or grapeseed like tumors 1 3 mm. in diameter The surface is flattened uneven and divided into lobules by fine whitish septa. In the cavernous final stage seen in about 5% of senile angiomas, solitary lesions are thin flaccid protruding blood filled bluish red occasionally pedunculated sacs 5 10 mm. in diameter Expansive growth or malignant degeneration of senile angioma was never noted. Predilection is for the trunk and proximal parts of the limbs and the mediothoracic and interscapular regions *but senile angioma may appear* anywhere on the body except the palms and soles

(4) Dermatologica 114:345-359 June, 1957

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(3) A.M.A. Arch. Dermat. 75:567-572, April, 1957

Clinically all the lesions behaved like benign tumors. Metastases did not occur but local recurrence was noted in 2 patients after incomplete surgical excision

Cutaneous Papillomas of Neck Papillomatous Seborrheic Keratoses. All dermatologists are aware of the morphologic characteristics of the tiny tags or papillomas that occur on the neck upper chest and eyelids during the middle and later years of life However microscopic description based on examination of a large number of these lesions has not been published Morris Waisman[6] (Tampa Fla.) reports his findings in the study of numerous cutaneous tags in all stages of development

Tiny lesions showed hyperplasia of the rete in some as a broadened acanthotic layer and in others as a folded structure associated with deep horny plugs of stratum corneum and prominent papillomatosis of the corium Sometimes rete cells showed perinuclear vacuolization but no indication was detected of verrucous characteristics Cells of the basal type were slightly increased in the distal portions of the epithelial ridges Melanin pigment occupied the cells of the basal layer to a variable degree Pigmented dendritic cells occurred in the cutis sparingly Typical regularly patterned prickle cells made up most of the rete The granular layer was of normal thickness. The connective tissue of the corium was usually fine, fibrillar and cellular Older tags showed progression and accentuation of the epidermal changes observed in the early lesions At this stage two general morphologic patterns could be separated an epidermal and a fibrous depending on which histologic component was ascendant Inevitably folding of the tissue and tangential planes of cutting exaggerated the multiplicity of cysts, papillae epidermal masses and epidermal strands produced by invaginations of the stratum corneum

The almost invariable association of seborrheic keratoses and cutaneous tags and the suggestive transitions of one form into the other prompt the impression that the papillomas are modified seborrheic keratoses The histopathologic changes of small papillomas resemble those of early lesions of seborrheic keratosis. If seborrheic keratoses are regarded as delayed epithelial nevi cutaneous papillomas should be accorded the same significance because they are similar le-

(6) South. M J 50 725-732, June, 1957

sions. Emergence of lesions during pregnancy and after the menopause suggests the possibility that the physiologic hyperactivity of the anterior lobe of the pituitary gland and the adrenal cortex common to both states may be responsible for their appearance.

It is not inferred that all tags of the skin are to be classed as seborrheic keratoses. The larger isolated smooth-surfaced tags are predominantly connective tissue outgrowths and may therefore be relegated to the group termed molluscum fibrosum, possibly in some instances having grown through and beyond a seborrheic keratosis stage. Most tags belong to the seborrheic keratoses but other excrescences may simulate tags clinically and sometimes require microscopic examination to distinguish them. These include digitate and filiform warts, mollusca fibrosa, papillomatous pigmented nevi, cutaneous horns and neurofibromas.

[The lesions discussed here by Waisman are among the more common conditions seen in dermatologic practice, yet have been investigated very little. Waisman's results strongly indicate that many of these lesions are either seborrheic keratoses or modified seborrheic keratoses or have gone through a phase of seborrheic keratosis. Nevertheless, we agree with Livingood and Ellis, who, in discussion of this paper, both preferred the use of the term "cutaneous tags" or "skin tags" over "papillomatous seborrheic keratoses." The etiology of these lesions remains unknown. —Eds.]

Clinical Appearance, Pathogenesis and Treatment of So-called Dorsal Cysts are discussed by Hans Gotz and Rudi Koch (Univ. of Munich). Dorsal cysts (also called synovial cyst, periarticular cutaneous fibroma, cystic nodule of digital joint, myxomatous degeneration cyst of the skin and subcutaneous tissue) are rare, mostly smooth, pea- to hazelnut-sized firm tumors with a predilection for the paraarticular tissues of the extensor aspect of finger and toe joints, i.e. interphalangeal, metacarpo- and metatarsophalangeal articulations (Fig. 48). They are partly transparent and slightly fluctuating. The color of the covering skin is mostly normal, occasionally slightly yellowish or livid. The cysts contain a gelatinous substance which after puncture can be pressed out but reforms once the puncture wound has closed. Dorsal cysts occur more frequently in females, are not painful and are often multiple and symmetrical.

There is no unanimity of opinion on the pathology of these tumors, which are variously assumed to be papillomas or erroneae with colloid degeneration of epithelial elements

71 Hautarzt 7 333 337 December 1956

synovial cysts originating from the articular capsule, periarticular fibroma with degeneration and cyst formation, myxomatous degeneration of the cutis associated with cyst formation in the synovial endothelium or due to increased secretory activity of fibrocytes which when slightly traumatized form the mucoid substance.

In their series of investigations the authors tried to elucidate the nature and pathogenesis of these cystlike formations Since no endo- or epithelial layer covering the cyst wall existed in the corium they are of the opinion that the formations should be called pseudocysts Contrast roentgenograms revealed no connection between pseudocysts and the articulation underneath Moreover histologic examination did not show degenerative transformation of collagen into the characteristic gelatinous substance Toluidine blue staining produced marked metachromasia of this substance, but metachromatic changes did not occur when sections had been treated with hyaluronidase. These findings indicate that the gelatinous contents of the pseudocysts consist of hyaluronic acid Microscopic examination of sections also revealed increased fibroblasts and mast cells It is assumed that by continuous stimuli connected with articular movements (structural changes of bones?) the local fibroblasts produce abnormal amounts of hyaluronic acid, which gradually separates collagen bundles and finally forms a "pseudocyst." This hypothesis is supported by therapeutic effects of hyaluronidase



Fig 48.—Fluctuating cyst on distal interphalangeal joint with secondary dystrophy of nail. (Courtesy of Gotz, H., and Koch, R Hautarzt 7:533-537 December 1956.)

In treatment of the pseudocysts incision, curettage and physical and chemical cauterization were recommended but could not prevent recurrences. Radium and x-ray therapy were also used. The authors tried successfully to liquefy mu copolysaccharides by injection of hyaluronidase 3 Schering units were injected into the pseudocyst and after a few minutes the liquefied contents removed by aspiration splint ban dage was applied for 1 week to the finger Five pseudocysts treated in this way did not recur during observat on periods of up to 8 months.

► [It is gratifying that the authors have taken the trouble to study and elucidate the natur of these lesions Gotz and Koch here propose relatively simple form of therapy which is certainly worth trial.—Eds.]

Sebocystomatoses are discussed by Hasan Oyal and Wolf gang Nikolowski[8] (Univ of Tub ngen) In typical cases sebocystomatoses involve the middle of the sternum and the scrotum e., mainly regions with particularly large and mul t loculated sebaceous glands. In these areas are groups of nodules which are firm, taut and mobile on the underlying tissues They are millet grain to pea sized or even larger flat o hemispheric, prom nent and skin colored, yellowish or livid On puncture they empty an o'ly viscous liquid. Comedones are occasionally present. Some observers deny any connections between sebocystomatosis and acne vulgari The authors observation, however of concomitant seborrhea oleosa, acne vulgaris, acne conglobata, milia, fa milial sebaceous cysts and dermatitis seborrheica, as well as the predilection areas of sebocystomatosis indicate a rela tionship to Darier's keratosis. Endocrine factors may also be of etiologic significance since sebocystomatosis is observed mainly between 10 and 30 years of age, i.e. from puberty (the period of hormonal changes) onward. In 1 case sebocystomatosis manifestations were said to have existed t birth and in nother to have followed trauma, namely ex t rpation of testis (mechanical obstruction of circulation?) The probabl congen tal case with cyst formation of the scrotum may be explained on the basis of fa lty dev lopment of sk dnexa, ce retention f the secretion alone can ha dly a cou t for formation of these cysts.

Histology evealş cysti ca t es of arious zes The n side f the cy t wall shows 2 or 3 layers of epithelial el ments co ered by projecting clear often foamy cells with

[8] Arch Der Syph Dermat 204 341 373, 1957

large, bright or missing nuclei and by flattened stretched lobuli of sebaceous glands Occasionally particularly in scrotal cysts of long standing the cyst wall may be partly even totally destroyed and replaced by *granulomatous tissue* containing large often bizarre histiocytes giant cells with foamy cytoplasm and rhombic empty spaces. Ducts of eccrine glands often seen near cyst walls never showed any connection with cyst lumens Neither were myxomatous-like changes of the connective tissue which often occur around sweat gland cysts observed. The epidermis above sebocystomatosis cysts is often thin its granulosum layer missing

In sebocystomatoses basal cell proliferation may be found within the cysts Real carcinomatous growth in sebocystomatosis has not been reported so far and was not observed by the authors

► [In the English-speaking literature these lesions are usually referred to as steatocystoma multiplex, the name given by Pringle in 1899—Eds]

Three Familial Cases of So-called Gunther's Sebocystomatosis (Hereditary Polycystic Epidermic Disease of Sézary and Levy Coblentz) are reported by Antonio Sapuppo[9] (Univ of Catania)

CASE 1—Woman, 48, in fair general condition and with no family history of dermatologic disease had parenchymatous nodules, the size of a chick pea and covered by yellowish skin, along the hairline at the temporal region and on the side of the neck. Some of the nodules along the hairline were larger and were characterized by bluish skin, missing hair and vascular ectasia. The lesions, present since the patient's youth were painless. Histologic study showed keratinization of the innermost layers of the cystic formations, which were separated from the epidermis by a thin clearcut layer of connective tissue They had a lamellar stratified content and around them were hair *follicles*, fragments of sebaceous glands and numerous blood and lymph vessels.

CASE 2.—Woman, 21 daughter of patient in Case 1 had lesions similar to those of the mother but involving also the trunk and extremities, since she was 16. They were either isolated, in groups of 2 or 3 or especially in the retroauricular area in conglomerates of numerous nodules *(Fig 49) several millimeters to several centimeters* in diameter Acne punctata and acne pustulosa were present. Histologic study showed cystic format ons with no content and no keratinization, *hair follicles, fragments of sebaceous glands*, vessels near the cystic wall and normal sweat glands.

CASE 3—Man 19 son of patient in Case 1 for 3 years had lesions and a skin condition much like those in Case 2. Histologic study was not made.

(9) Minerva dermat 31:294-305, October 1956.



Fig 49 (Courtesy of Bergerre, A Minerva dermat 31 294 303, October 1956)

The a thor suggests that these lesions originate in ele ments of the first epithelial germ wh ch can be related to the hair follicles or completely independent of them. He feels that the condition ought to be called hereditary polycystic epiderm c disease of Sérary and Levy-Coblentz because this name ndicates th origin and the main clinical aspects of th d sease

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6 FUNGOUS INFECTIONS

Mycotic Infection of Hands was found by Poul V Mar cussen (Copenhagen) in 1 of 425 patients with eczematous nd intertriginous lesions of the hands and feet. Scrapings from ll ffected skin reas and from the nail and nail groove of the 5th toes and 4th interdigital spaces were cultured and xamined by direct microscopy All patients with mycosis of the hands had intertriginous changes in one or more inter digital spaces. Cultures showed Trichophyton mentagrophytes in 8 patients nd T rubrum in 1 Mycosis of the hands was equally f equent among patients with nd w thout mycosis of th feet. I 3 of 5 patients with mycosis of the hands and feet, the infection was first noticed on the feet, whereas in 2 t was first noticed simultaneously on hands

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least 1 other area showed positive. Co-existence of infections in different loci of the foot has obvious implications in interpreting periodic recurrences, particularly in the interdigital area. There is no need to look for an exogenous source of infection because the nearest most abundant source is within the foot itself. Findings indicate the advisability of treating the whole foot to eliminate acute recurrences. It is however practically impossible to cure onychomycosis or chronic infections of the sole.

By clinical criteria alone, diagnosis of actual fungous infection was correct most often on the soles (about 95%), next in the intertriginous areas (about 75%) and least in the nails (about 65%). The most reliable sign of onychomycosis is piling up of subungual keratin, which gives the nail a thickened, distorted appearance. Simple discoloration, fraying and minor architectural alterations may or may not be associated. When infection is not suspected on clinical grounds, fungi occur as inapparent infections most often in the nails and soles (about 25-30%) and least often in the intertriginous areas (about 10%). When all interspaces are clinically normal, fungi rarely are detectable in scrapings. They sometimes can be found, however, in clinically normal interspaces when there is accompanying clinical infection in other interspaces.

The authors were able to establish experimental intertriginous infections with great difficulty in normal subjects. When there was an accompanying pre-existing infection of the foot, the percentage of successful inoculations was greater. Necessary conditions for infection are persistent moisture and massive exposure to the pathogens. Spontaneous regression is the rule in experimental infections after removal of the predisposing causes. Skin sites that already were inflamed and excessively macerated (due to nonmycotic intertrigo) were resistant to experimental fungous infection.

Trichophyton Rubrum Infection in Families. Mary P. English[3] examined the family contacts of 19 patients with T. rubrum infections. In 9 families, more than 1 person was infected with the organism and within each family the isolates were mycologically of the same type. Of 48 contacts examined, 13 (27%) were infected. In 11 of these the infection was first noticed on the feet. Minimum duration of ex

(3) Brit. M. J. 1:744, Mar. 30, 1957

and feet. In patients mycosis of the hand was bilateral.

Of 183 patients with verified mycosis of the hands and/or feet 2 had deformities of the interdigital spaces of the hands following disease or accident and both had mycosis of the hands. Two patients were engaged in occupations resulting in compression of the interdigital spaces (salesmen who carried heavy bags all day) and both had fungous infections of the hands. Four of 7 patients working with fat solvents and 4 of 46 engaged in moist work had mycosis of the hands. In all other occupational groups no hand infections were found.

The author concludes that mycosis of the feet is probably not an important source of mycotic hand infections but that certain occupations predispose to such lesions.

► [*The editors' clinical experiences are entirely in agreement with the results of Marcussen's timely study. Dermatologists are well aware of the frequency with which eczematous and other hand eruptions are misdiagnosed, especially by those not well trained in diseases of the skin. This holds true particularly for dermatoses involving both the hands and feet. All eczematous eruptions of the toes and interdigital spaces then are liable to be indiscriminately called "athlete's foot" and those of the hands an "id" eruption. Of the 420 patients with eczematous eruptions of the hands and feet investigated by Marcussen, fungi could* not *be demonstrated on the feet of 244 (58%). This finding, together with the very low incidence of associated fungous infections of the hands, once more makes it obvious how essential it is to consider in differential diagnosis the many eczematous and noneczematous dermatoses, other than epidermophytosis, which affect the hands and feet. Unless the correct diagnosis is made, it is impossible to institute the best available specific and/or nonspecific therapy.—Eds.*]

Experimental Study of Tinea Pedis and Onychomycosis of Foot is reported by John S. Strauss (Boston) and Albert M. Kligman[3] (Philadelphia). Preliminary studies of both feet of 100 prison inmates showed the diagnostic superiority of the KOH examination. Correlation between 377 cultures and direct examinations showed that in 77% of the cases there was agreement, positive or negative, but in 23% the KOH examination was far superior. Only 2% of positive samples would have been missed if no culture had been done whereas 23% would have been missed if the KOH examination had been omitted. Isolated fungous infection of 1 region of the foot was the exception. Regardless of the area chosen as a reference point, be it the nails, soles or interdigital spaces, if it is KOH positive a positive KOH will be found in about 65-75% of the other areas examined. In 50% of the cases the other 2 areas of the foot were positive, in 85% at

(3) A.M.A. Arch. Dermat. 6:70-79, July 1 57

sults would hav been in control series of patients, e.g., the family members of 32 psoriasis or hand-eczema patients living in the same community What is the incidence of symptomatic and asymptomatic fungous infection in such control series Only with these additional data can valid conclusions be drawn from an epidemiologic survey of T rubrum infections in families —Eds.)

Investigation of Epidemiology of Epidermophytoses Particularly of Trichophyton Rubrum (Castellani) is reported by Ferdinand Fegeler[1] (Univ of Munster) The epidermophyton group was previously assumed to include Epidermophyton floccosum (inguinale) which exclusively invades the epidermis T mentagrophytes var interdigitale (also previously called E. kaufmann-Wolf) found mai ly in the epidermis less often in nails and rarely in hairs and T rubrum (Castellani) cultivated mostly from nails but also from epidermis and hairs. Recent investigations disclosed a decreased occurrence of F floccosum and a considerable increase of T rubrum up to 63 nd 70% of dermatophytes ascert ined by culture exami ation. These findings were ch efly explai ed epidemiologically

The author's series of mycologic experiments not only confirmed the increasingly frequent occurrence of T rubrum, but it was seen that the fungi were found oftener in finger than in toenails a d also in other parts of the body e g in previously often misdiagnosed follicular trichophytosis of the legs Further considerably ncreased findings of T rubrum were seen since cycloheximide agar was used. This not only promotes pigment formation by T rubrum a d f cil tates the diagnosis but also nh bits the concomitant bacterial flora because of the presence in the agar of added penicillin, streptomycin and cycloheximide

Three types of T terdigitale exist cerebriform granu lar a d pleomorphous. In previous experiments it was shown that under certa n conditions the pleomorphous type produced pigment and could not be differentiated from T rubrum After cycloheximide agar was used the pleomorphous type without pigment production was no longer observed. Similarl with the granula type pigment production could be obtained by cult vation on cycloheximid agar or on ad d tion of Achromycin (1,000-10 000 γ/cc.) to the cultu e medi m These findings suggest the capability of T nter digitale to change morphologically (granular pleomorphous varieties) or biologically (pigment production) and to eact

[1] Arch klin exper Dermat 203 576 5 6, 1956.

posure before signs of infection appeared was 1 year One patient was exposed for 15 years before infection was apparent Six out of 8 persons over age 14 who had been exposed during childhood had contracted the disease Seven of the original patients could trace their initial infection to residence or active service abroad In 4 others the disease was first noticed while the patient was using swimming baths regularly or taking active part in sports. Five families had for 3 years or more taken precautions against spreading the disease including avoidance of walking about with bare feet, exchanging footwear or using a communal bath mat. When beds were shared socks were worn. After precautions were instituted the infection did not spread in these families.

In the total group of 32 infected persons (19 original patients and 13 infected contacts) in 27 the initial infection occurred on the feet. The hands alone were involved in 4 patients and 1 child had a lesion on the face. The nails were infected in 25 (78%) persons Three women and 4 men had groin infections. One woman had infection of the axilla and 1 had extensive infection of the arms and legs. Four patients had ringworm of the face and body Dermatophytes other than T rubrum were encountered only twice each time in association with T rubrum

In view of the long exposure period before clinical infection with T rubrum becomes evident it is probable that breakdown in personal immunity precedes onset of the clinical disease. If a person is to become infected, this lessening of immunity must coincide with inoculation with a viable fungus. The intractability of T rubrum infections to treatment their disfiguring nature and the mental distress that often ensues emphasize the importance of attempting to check spread of the disease This is especially true in families with young children as shown by the high rate of infection in persons exposed in childhood Precautions should be simple and have the object of preventing the shedding of infective particles in places where others may come in contact with them. Sterilization of footwear and floors is impracticable and is not likely to be performed faithfully by the patient

► [Several factors interfere with proper evaluation of this study The author did fungous examinations only on those family members who had clinical symptoms and thus failed t ascertain incidence of symptomatic infection among the contacts. Furthermore it essential to know what re-

sults would have been in control series of patients, e.g. the family members of 32 psoriasis or hand-eczema patients living in the same community. What was the incidence of symptomatic and asymptomatic fungous infection in such control series? Only with these additional data can valid conclusions be drawn from an epidemiologic survey of T. rubrum infections in families.—Eds.]

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The author's series of mycologic experiments not only confirmed the increasingly frequent occurrence of T. rubrum but it was seen that the fungi were found oftener in fingernails than in toenails and also in other parts of the body, e.g. in previously often misdiagnosed follicular trichophytosis of the legs. Further considerably increased findings of T. rubrum were seen since cycloheximide agar was used. This not only promotes pigment formation by T. rubrum and facilitates the diagnosis but also inhibits the concomitant bacterial flora because of the presence in the agar of added penicillin, streptomycin and cycloheximide.

Three types of T. interdigitale exist: cerebriform, granular and pleomorphous. In previous experiments it was shown that under certain conditions the pleomorphous type produced pigment and could not be differentiated from T. rubrum. After cycloheximide agar was used the pleomorphous type without pigment production was no longer observed. Similarly with the granular type pigment production could be obtained by cultivation on cycloheximide agar or on addition of Achromycin (1,000-10,000 γ/cc.) to the culture medium. These findings suggest the capability of T. interdigitale to change morphologically (granular pleomorphous varieties) or biologically (pigment production) and to react

Arch. klin. u. exper. Dermat. 203: 170-174, 1956.

in vivo to aggravated alimentary and living conditions.

The increasingly frequent observation of T rubrum may be explained epidemiologically but also by biologic properties of the fungus and improved mycologic technics Apparently T rubrum and T interdigitale are not separate species but varieties of T mentagrophytes.

► [The enhanced growth of pathogenic fungi planted on agar media to which cycloheximide and various antibiotics have been added has proved a distinct aid to the dermatomycologist.

In the early years when penicillin was introduced for systemic use it was not unusual to see a flare-up of dermatoses of feet, hands and genitocrural areas. This flare-up was reported as possibly being an "id" type reaction of areas which were or had been the sites of a fungous infection and was believed to be due to a cross-sensitization between allergenically similar components of the penicillin molds and dermatophytes. Although there is still no convincing argument against this theory the possibility might also be considered that such "id" like flare-ups may have resulted from suppression by penicillin of bacteria which were antagonistic to the dermatophytes in the affected areas.

We have the impression that few dermatomycologists would agree that T rubrum and T interdigitale are varieties of T mentagrophytes.—Ed.]

Etiology of Dermatophytosis Shift from Trichophyton Mentagrophytes to Trichophyton Rubrum, 1935-54 Irwin L. Maskin Claire L. Taschdjian and Andrew C. Franks[5] (New York Univ Post-Grad Med. School and Skin and Cancer Unit) reviewed the records of the Mycology Section of the Unit for 1935-54 During this period, 3 182 positive cultures were obtained in patients suspected of having dermatophytosis. Trichophyton mentagrophytes T rubrum and to a lesser degree, Epidermophyton floccosum were the organisms found in most cases

Between 1935 and 1954 T mentagrophytes was superseded by T rubrum as the predominant etiologic agent. Isolations of T mentagrophytes/100 cultures of dermatophytosis dropped from 80% in 1935 to 20% in 1954 while the reverse was true for T rubrum In terms of incidence T mentagrophytes dropped from a high of 13% of cases of clinical dermatophytosis in 1937 to 2% in 1954 whereas infection due to T rubrum rose from 1 8% in 1935 to 10% in 1954 Incidence of E. floccosum remained at a fairly steady low 1% and cultures isolated at 3-10%

Review of the literature indicates a world wide and a nation wide increase in T rubrum infections in recent years The reasons for this increase and for the decrease in T mentagrophytes infections are unknown. A contributing factor

(5) A.M.A. Arch. Dermat. 75 44-49 January 1957

might be the extremely resistant chronic type of infection produced by T rubrum, which may transform the patient into chronic carrier who is more likely to disseminate the disease over a period of years than is the patient infected with T mentagrophytes. It is also possible that the organism itself may be changing in virulence, or it may be taking advantage of a world-wide decrease in local and general body resistance induced by wars and economic depressions

Rubrophytia. Increasing occurrence of infections due to Epidermophyton rubrum in Prague and its vicinity was observed by Jan Obrtel[1] since 1950 Among 115 patients, the lesions were located in the interdigital areas and nails of the feet and hands in 52% in 28% the distribution was similar but additional lesions were found elsewhere, and in 20% the toes or fingers were not involved. With these infections, the pruritu was more intense than that seen in infections with other fungi, but no allergic reactions were observed. Clinically the lesions were indistinguishable from other dermato- and onchyomycoses but the diagnosis was suspected if several toes or fingers were involved or the nails were elevated from the hyperkeratotic nail beds. Lesions located in the folds of the skin usually extended to the periphery and their serpiginous and discontinuous margins were formed by macular and papular lesions In the later stage, the papular lesions tended to disappear the skin underwent lichenification and fine scaling occurred. This course was particularly characteristic in perianal and perigenital lesions. Hyperkeratotic forms were observed in 8 and vesicular forms in 2 patients.

The best therapeutic results were obtained with chrysarobin despite the fact that this substance was found ineffective in vitro Chrysarobin in 0 5-1% solution or 0.5% ointment was applied twice daily for 6 days discontinued for 2 days and then resumed for another 6 days in the form of 1% ointment Application of strong keratolytic agents preceded the chrysarobin therapy in cases of onychomycosis. Prolonged use of fungicidal powders was recommended after completion of chrysarobin therapy

► [It is remarkable that despite the continuous search for new and more effective topical fungicides none have been found that regularly are better than some of the "old-fashioned" remedies and none have been found that are truly fungicidal in vivo Just as chrysarobin and anthralin (cignolin)

1 [illegible] dermat. [illegible]

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(5) A.M.A. Arch. Dermat. 75:64-69 January 1957

their growth but actual growth has not been shown. It is concluded that direct sampling is more satisfactory for isolating dermatophytes from floors than any method previously described.

► [Using new technic plus medium containing Acti-dione, penicillin and streptomycin, Gentles has succeeded where others failed or had success only in exceptional instances. Previous failure to recover dermatophytes from bathroom and shower room floors, of course, was due only to technical deficiencies and not to absence of dermatophytes. This was clearly demonstrated by S. Rosenthal and the senior editor when they showed that fungi often can be recovered from the foot-bath water not only of persons with active fungous disease but even from persons with asymptomatic fungous infection. However, as has often been pointed out before, proof is entirely lacking that exposure to these fungi on the floors of shower rooms, etc., will cause acute fungous disease on the feet of persons without active fungous disease.—Eds.]

Epidemiologic and Clinical Investigations on Onychomycoses. Recent communications from various European countries indicated not only a remarkable increase of onychomycoses but also that in most cases onychomycotic changes were caused by Epidermophyton rubrum (Castellani). Confirming these reports, Hildegard Langer* (Univ. of Berlin) states that the number of onychomycoses cases seen in the clinic increased from 188 (18.6% of all dermatomycoses) in 1955 to 233 (28.2%) in 1956. In 166 of 318 cases, the cultures were positive: in 136 (82%) E. rubrum was found, in 8 (4.8%) E. interdigitale (Kaufmann-Wolf) and in 9 (5.4%) various trichophyton strains (Trichophyton rosaceum 6, T. cerebriforme 2, T. gypseum 1) were isolated. Scopulariopsis was found in 6 and Candida albicans in 2 cases. The latter has been said not to be able to affect keratin but Ehrmann and Weidmann proved that nail substance itself can be attacked by candida strains. Double infections (E. rubrum and Scopulariopsis brevicaulis and fusca respectively, E. rubrum and T. faviforme, C. albicans and C. tropicalis) were observed 3 times. In epidermophytosis without nail involvement, 78 positive cultures were obtained, of which 51 showed E. rubrum, 25 E. interdigitale and 2 E. inguinale. In trichophytosis T. faviforme was isolated in 17 cases, T. gypseum granulosum in 14, T. gypseum asteroides in 9 and T. rosaceum in only 1.

The clinical manifestations of onychomycoses corresponded to those described in textbooks. They were observed

(*) Arch. klin. u. exper. Dermat. 204 434-434, 1957

still proves effective so do the original Whitfield's ointment and its modification as a tincture resorcin and sulfur shake lotions and other keratolytic and peeling preparations. In Trichophyton rubrum infections of the body anthralin preparations are our preference.—Eds.]

Tinea Cruris in Women Report of Three Cases. According to Mary P English and C J La Touche[7] these represent the only cases observed at their clinics during periods of 2 and 7 years respectively All were due to Trichophyton rubrum probably reflecting the pronounced rise in incidence of T rubrum infections in recent years. One source of infection for tinea cruris probably is an autogenous one, such as a tinea pedis lesion This could account for preponderance of tinea cruris in men since there apparently is greater incidence in men than in women This might possibly be due to some intrinsic biochemical difference connected with sex, but the more likely explanation is that men are more often exposed to infection It also is possible that many women with tinea cruris do not report for medical care

► [It is our impression that widespread tinea corporis due to T rubrum also is more common in men than in women. As a matter of fact, in our private practices we recall seeing only men with widespread T rubrum infections on the body.—Eds.]

Isolation of Dermatophytes from Floors of Communal Bathing Places J C Gentles[8] (Univ of Glasgow) describes a direct sampling method that showed spread of infection among coal miners took place in bath houses used by them A special disk with padded surface properly autoclaved, was used to obtain samplings from the floors Each disk pad then was used to inoculate 3 Petri dishes of 4% malt extract agar supplemented with 20 units/ml penicillin 40 units/ml streptomycin and 0.5 mg/ml Acti-dione® Routine incubation at 28 degrees was carried out and examinations made at intervals of 2-3 days Trichophyton mentagrophytes appeared after 7 10 days and T rubrum after about 3 weeks.

Using this technic parasitic fungi were grown from samplings taken from the floors of all 5 bathing places tested. From 87 samplings 9 colonies of T mentagrophytes were grown and 2 colonies of T rubrum Whether the dermatophytes are present on the floor as saprophytes or in skin fragments is not clear It has been shown by Peck et al that dermatophytes can exist for long periods on concrete floors and that the pH of aged concrete floors is compatible with

(7) Brit. J Dermat. 69:311-314, September 1957
(8) J Clin. Path. 9:374-377 November 1956.

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(9) Arch. klin. u. exper. Dermat. 204:424-436, 1957

mostly in middle-aged persons and oftener in women than in men In children up to 10 years mycotic nail changes were seen only twice

The pathogenesis of onychomycosis is still rather obscure Along with the mycotic infection exposure to trauma (eg in housewives) vascular disturbances trophoneurotic changes hyperhidrosis of the feet and hands, hormonal and even nutritional factors may possibly play an important role.

► [The increasing trend to T rubrum infections has now been reported from many countries. In our onychomycosis material, also, the incidence of T rubrum infections by far outnumbers infections with other species of fungi. However at the New York Skin and Cancer Unit, we have not had any substantial increase in onychomycosis cases in recent years, as has occurred in Berlin.—Eds.]

Trichophytin Reaction after Exposure to Dermatophytes and of controls not exposed to fungi is reported by Hymen Roguchefsky Stanley A Rosenthal Jerome Z Litt and Rudolf L. Baer[1] (New York Univ Post-Grad. Med. School and Skin and Cancer Unit) After first being tested with trichophytin 72 subjects immersed the feet in fungus-contaminated foot baths Six or more weeks later they were retested with trichophytin The same trichophytin testing without immersion was performed on 43 controls Testing was carried out for immediate urticarial response with 0 01 ml trichophytin on one arm and control extract on the other For the delayed 48-hour response, 0 1 ml was used.

Of 63 exposed subjects with a negative immediate reaction, 8 (12.7%) showed a positive immediate reaction in the repeat tests whereas of 40 controls only 1 (2 5%) had a positive immediate reaction in the repeat tests Of 47 exposed subjects with a negative delayed 48-hour reaction 19 (40 4%) had a positive delayed reaction in the repeat tests but of 18 controls only 4 (22.2%) had a positive delayed reaction in the repeat test Of 38 exposed subjects with negative reactions in both tests 20 (52 6%) showed reactions on retesting compared with 3 (20%) of 15 control subjects It is suggested massive fungus exposures can produce or awaken trichophytin sensitivity without causing clinical fungous disease although other mechanisms also might account for the changes in the trichophytin reactions observed

► [These findings parallel those in other asymptomatic infections. For example, most persons who have a positive tuberculin reaction acquire this without clinically manifesting disease.—Ed]

(1) A.M.A. Arch Dermat. 74 606-609 December 1956.

Observations on Rural and Urban Ringworm are reported by Lucille K. Georg, Eugene A. Hand and Robert A. Menges[1] (US Dept. of Health, Education and Welfare At lanta, Ga.) Distribution of the dermatophyte genera among 173 patients studied was trichophyton, 97 (56%) microsporum, 71 (41 1%) and epidermophyton, 5 (2.9%) In rural ringworm, infections were caused by Trichophyton verrucosum and T mentagrophytes. In urban ringworm, causes were Microsporum audouini, M canis, T tonsurans T mentagrophytes (downy variety) T rubrum and Epidermophyton floccosum. In rural ringworm children showed scalp lesions primarily and body lesions secondarily men showed lesions of the beard area and the face and women showed lesions on the smooth skin of exposed areas of the body Tissue reactions usually were suppurative (kerion) generalized reactions ften occurred also Many of these patients had a history f contact with ringworm-infected cattle or ringworm in some other farm animal Urban ringworm has been caused primarily by M. audouini although there have been many cases of T tonsurans infection, both occurring mostly in children and mostly on the scalp This latter group gav history of contact with other nfected human beings rather than with animals.

In rural ringworm, T verrucosum appears to be almost entirely of bovin origin. Lesions on cattle vary from slight scaling nd loss of hair to thick, hard, gray-to-brown crusts. Lesions from T verrucosum infection may be acquired indirectly by contact with objects that were contacted by the infected animal. Infections of T mentagrophytes may come from large farm animals, such as cows or horses, but small nimals also are a source. Rodents are an important reservoi of this fungus and play an important part in its transmission. Trauma or pre-existing skin lesions in human beings increase their susceptibility to fection.

In urban ringworm, the 2 epidemic types, those of M audouini a d T tonsurans, are anthropophilic in nature and are tran mitted from person to person. The T tonsurans type has occurred especially n areas where there are itinerant Mexican workers. Among city dwellers, especially among those living under conditions of close association with other people T rubrum T mentagrophytes (downy

(1) J Invest Dermat. 27 331 352, November 1956.

variety) and E. floccosum occur The M canis infections are largely of animal origin dogs and cats and the disease is readily transmitted to human beings.

Generally speaking rural ringworm is primarily of animal origin and urban ringworm is of the human epidemic type except for the M canis infections which are contracted from dogs or cats.

► [Ordinarily zoophilic pathogens tend to produce deep, extremely inflamed lesions (e.g. kerionic responses) in man and are not highly infectious from man to man. Anthropophilic pathogens, however tend to cause superficial lesions with little inflammation in man, but usually they are highly infectious from man to man.—Eds.]

Detergents in Mycology A study on the fungicidal properties of detergents and their use in direct mycologic examinations is reported by G Achten[1] (Univ of Brussels) The two most active fungicidal detergents tested were alkaline alkylsulfosuccinate (Synkapon) and dodecylbenzene sodium sulfonate (Tensaryl 80 B) In a concentration of 0.01% in vitro they completely suppressed the dermatophytes studied suggesting a possible therapeutic value

A clarifying detergent for use in direct mycologic examinations should fulfil the following requirements (1) sufficient clearing of scales, nails and hair (2) immediate staining of filaments and spores (3) simultaneous bacteriologic and mycologic examination (4) it must be possible to reculture dermatophytes in Sabouraud s medium (5) absence of artefacts and (6) preparation of demonstration slides.

The procedure used for the study of scales hair and nails is identical with that using potassium hydroxide, but does not require heating A drop of aqueous detergent solution (0.1%) and stain (0.2%) is added to the specimen on a sterile slide and examined microscopically Basic fuchsin and Bismarck brown are the most satisfactory stains for this purpose

Of four detergent tested alkyl dimethylbenzylamine (Ammol U C B) hexaethyleneglycol stearate (Belsam U C B) cetyldimethylbenzylammonium chloride (Tensia) and cetylostearic alcohol (Tensactol SX Tensia) the last appears the most satisfactory because it permits the most uniform staining of cell and dermatophyte with 100% positive cultures.

► [A few years ago Mandel, Muskatblit, Frank and Herrmann, at the New York Skin and Cancer Unit, showed that sodium lauryl sulfate could be used as a clearing agent for microscopic examination of material taken

(1) Dermatologica 114:360-367 June 1957

from fungous infections of the skin. Moreover this clearing agent, in contradistinction to potassium hydroxide, did not interfere with the use of the microscopically positive specimens for culture on Sabouraud's medium. Apparently their method was not sufficiently effective or reliable to have become generally used. More extensive trials with the detergents suggested by Achten' study are warranted, since they apparently are not only highly effective for clearing of scales and hairs but positive cultures result in 100% of the cases when the microscopically positive specimens are planted on suitable mediums.—Eds.]

Use of Cycloheximide-Chloramphenicol Medium in Routine Culture for Fungi. In mycologic examination of 719 scrapings from 600 subjects, Stanley A. Rosenthal and Domenica Furnari (New York Univ Post-Grad Med School and Skin and Cancer Unit) found cycloheximide-chloramphenicol agar to be superior to Sabouraud's agar as an isolation medium. By use of this medium contaminated tubes were reduced by more than 50% and isolation of dermatophytes was increased by nearly 100%. Gross and microscopic morphologies of the dermatophytes were not altered by inclusion of 100 mg. cycloheximide and 50 mg. chloramphenicol/L. of medium. Cryptococcus neoformans, Allescheria boydii and Aspergillus fumigatus appear to be the only human pathogenic fungi inhibited by cycloheximide at the concentration used.

In this study 66 cultures were isolated on cycloheximide agar but not on Sabouraud's medium. In only 4 instances were dermatophytes isolated on Sabouraud's agar when the corresponding tube of cycloheximide agar was negative. The superiority of the antibiotic-containing medium was especially apparent in culturing material from the scalp, foot, nail and nail bed. The cycloheximide medium allowed for isolation of at least twice as many Microsporum audouini and Trichophyton mentagrophytes cultures and more than 3 times as many T. rubrum cultures as would have been isolated on Sabouraud's medium alone.

Because of its demonstrated superiority the fortified medium has replaced standard Sabouraud's agar as the medium of choice in routine diagnostic mycology at the New York Skin and Cancer Unit.

[The cycloheximide-chloramphenicol medium has proved to be a distinct advance in laboratory investigation of fungous diseases.—Eds.]

Semi-In Vivo Procedure for Testing Antifungous Agents for Topical Use is described by M. M. Dolan, J. S. Ebelhare, A. M. Kligman and R. C. Bard (Philadelphia).

J. Invest. Dermat. 28:367-371, May 1957.
Ibid., pp. 359-362.

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(1) Dermatologica 114:340-347, June, 1957.

scopic examination and cultures were taken from the oral cavities of clinically healthy adults with or without teeth infants diabetics, cachectic patients from cavities resulting from tooth extraction and from tonsillar crypts. Smears were applied to (1) Sabouraud s medium with penicillin and streptomycin to prevent bacterial growth (2) Sabouraud s medium without penicillin nd streptomycin to a oid inhibition of actinomyces, streptomyces or nocardia and (3) into liquid, oxygen-free th oglycolate medium (Brewer)

Of 230 cultures obtained 71% exhibited mycotic growth in 34% Candida albicans was found Candida species were demonstrable 114 times (C. albicans 78 C. krusei 9 C tropicalis 8 and C albicans stellatoidea 5 times) Rhodotorula species were isolated 6 times, Trichosporon cutaneum 7 and Geotri h m candidum 5 times the last mentioned may turn pathogenic. Saccharomyces cerevisiae was found in the mouth 3 times probably introduced with foods. Actinomyces israeli, a normal saprophyte of the oral cavity was isolated 15 times (5 times from tonsils, once from a cachectic patient and once from the cavity resulting from tooth extraction) Whether nocardia species are oral saprophytes is not known. Nocardia asteroides was cultivated only once from a cachectic patient Streptomycetes were found 22 times. Aspergillus pecies were seen in 30 smears and Penicillium citrinum, whi h so far has not been described as occurring in the oral cavity was often found. Whether the other 13 aspergillus species are regular oral saprophytes remains to be clarified.

The uthor point out that microscopic and cultural findings of C albicans do not justify the diagnosis "thrush, because C albicans and other cand da species were observed nearly regularly l pemphigus chronicus vulgaris chronic lupu erythematosu pemphigoid lichen rube planus, leukoplakia, etc Recent frequent eports of the higher incidence f thrush therefore, appear doubtful.

* [Few dermatologists would make diagnosis of thrush merely on the basis of an isolated colony of C albicans, without the presence of clinical changes suggestive of this disease —Eds]

Ulcerogummatous Candida Albicans Infection of Glans Penis. Superficial vesiculopustular manifestations of C. albicans infections of the kin and mucous membranes are more often observed than the rare, deep-seated granulomatou processes, during the course of which ulcerations may

METHOD.—Material for the test is obtained by infecting guinea pigs with Trichophyton mentagrophytes. The usual infection cycle consists of appearance of erythema within 4 days and many scales within 8-9 days. These scales are easily removed with a dull scalpel or razor blade. They are collected and stored in the ice box for use any time within 3 months. About 30 scales are placed in a stainless steel tissue capsule lined with no. 80 mesh wire. The capsule is immersed in a solution of the test compound for the first of several time intervals. When the first period has elapsed, the capsule is removed, rinsed with suitable solvent, then with distilled water. The capsule is opened, the scales removed and cultured on a Sabouraud's agar plate. The capsule is returned to the test solution until the next time interval has elapsed and the process of rinsing and removal of scales is repeated. The agar plates containing the scales are incubated at 30 C. for 10 days and presence or absence of growth recorded.

It is essential that the solvent used for the test compound is tested by the same procedure to determine its fungicidal effect. Each antifungous agent may be tested at the desired concentrations in as many solvents as are suitable for dermatologic preparations. Infected human scales or hairs may be substituted if available and desirable. The method permits measurement of the intrinsic antimycotic activity of a compound in a simulated clinical situation involving fungous infected skin. Physical and chemical factors affecting keratin penetration and compound reactivity with skin components are included in the measurement, providing some parallelism to actual clinical conditions.

Using this method, the authors obtained best results with undecylenic acid in polyethylene glycol 200, caprylic acid in propylene glycol and phenyl mercuric nitrate in aqueous solution. No growth was present with immersion times as short as 15 minutes. Isopropyl and ethyl alcohols were observed to kill the fungus within 5-15 minutes' immersion time, whereas polyethylene glycols and propylene glycol in concentrations of 5-100% did not kill the organism within 1 hour's immersion time.

► [Thus far, not one of the many semi-in vivo or in vitro methods suggested for testing topical antifungous medicaments has proved to be a reliable measure of actual clinical efficacy. However, every new effort to find an effective in vitro or semi-in ... method is welcome.—Eds.]

Fungous Flora of Oral Cavity was studied by T. Heymer and R. Doepfmer[6] (Univ. of Wurzburg). Since little is known about which fungi live in the mouth as saprophytes and which of these may turn pathogenic, smears for micro-

(6) Arch. klin. ... exper. Dermat. 204: 374-383, 1957.

scopic examination and cultures were taken from the oral cavities of clinically healthy adults with or without teeth, infants, diabetics, cachectic patients, from cavities resulting from tooth extraction and from tonsillar crypts. Smears were applied to (1) Sabouraud's medium with penicillin and streptomycin to prevent bacterial growth (2) Sabouraud's medium without penicillin and streptomycin to avoid inhibition of actinomyces, streptomyces or nocardia and (3) into liquid, oxygen free thioglycolate medium (Brewer)

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The authors point out that microscopic and cultural findings of C albicans do not justify the diagnosis "thrush" because C. albicans and other candida species were observed nearly regularly in pemphigus chronicus vulgaris, chronic lupus erythematosus, pemphigoid lichen ruber planus leukoplakia etc Recent frequent reports of the higher incidence of thrush therefore, appear doubtful.

► [Few dermatologists would make diagnosis of thrush merely on the basis of an isolated culture of C. albicans, without the presence of clinical changes suggestive of this disease —Eds.]

Ulcerogummatous Candida Albicans Infection of Glans Penis. Superficial vesiculopustular manifestations of C. albicans infections of the skin and mucous membranes are more often observed than the rare, deep-seated granulomatous processes, during the course of which ulcerations may

occur A case of the latter type involving the glans penis is reported by Marianne Thal[7] (Berlin)

Man, 57 had had tuberculosis of the vertebral column 12 years before hospitalization. There was no history of venereal disease. Ten months before admission, indolent flat nodules appeared on the glans penis which soon showed a central pustule followed by a deep, pea to penny-sized, torpid ulceration with slightly undermined borders and smeary coating of the base. Some lesions had healed, but new ones formed. On admission, the glans penis showed apart from numerous cicatrized defects a lentil-sized ulcer surrounded by an inflammatory infiltrate on the right half and a fresh infiltrate of about the same size on the left half (Fig 50) Bacteriologic, serologic



Fig 50 (Courtesy of Thal, M Dermatologica 114 368-373 June 1957)

and histologic examinations excluded soft chancre Plaut Vincent symbiosis, syphilis, tuberculosis diphtheria, lymphogranuloma venereum blastomycosis sporotrichosis and periarteritis nodosa. Finally C. albicans was cultivated, and with the aid of the serologic examination for monilia antibodies (method Janke) confirmed. Electrosurgical and potassium iodide treatment effected complete healing

Further mycologic analysis confirmed the diagnosis of C albicans (Robin) Berkhout and a chorioallantoic test with 5-day-old chicken embryos (the embryos died after 2 days) showing typical changes C. albicans could be reculti ated from the blood, yolk sac and l er In an animal experiment, 3 ntravenously inoculated mice died after 36 hours the microabscesses in their kidneys were caused by C. albicans.

► [Certainly C. albicans would have been one of the last etiologic possibilities to be considered for a destructive lesion f this type. If it ctually was the primary organism, the infection in this case either was due to an unusually pathogenic organism or occurred in an extraordinarily susceptible patient. It would have been highly desirable to have the results of his

(7) Dermatologica 114:368 373 June 1957

tologic examination in addition to the microbiologic and serologic tests. This patient had had active bone tuberculosis some years before. Among the possible diagnoses which would have to be considered and which could not have been ruled out by Thal' examinations are certain infectious granulomatous processes.—Ed.]

Investigations on Practical Use of Chorioallantoic Test for Differentiation of Yeast are reported by H Gotz, Th. Nasemann and H. C. Sturde[8] (Univ of Mun ch)

METHOD.—The chorioallantois of partly hatched eggs was inoculated with yeasts. From cultures which developed, small particles were used for (1) recultivation of yeasts on beerwort agar or Grütz III culture medium, (2) microscopic examination of smeared and crushed preparations (In 9 parts 10% potassium hydroxide and 1 part Parker Superchrome ink) and (3) histologic examination (hematoxylin-eosin (HE) and periodic acid-Schiff (PAS) stains) Yeast strains were recultured from organs of dead embryos 0.3 cc. yeast suspension (1 loopful culture material/1 cc. 0.85% N Cl solution) was injected into the peritoneal cavity of white mice electron-microscopic examination followed. Particles from protruding chorioallantoic cultures were carefully dabbed onto Zaponlac varnished platinum slides which were repeatedly washed with double-distilled water dried with the thermostat at 60 C. and examined.

A total of 375 eggs were inoculated with 19 yeast strains (44 laboratory strains) Chicken embryos died only in eggs inoculated with Candida albicans strains. When undiluted suspensions of C albicans were inoculated, the embryos died in 90% of the egg cultures within the first 5 days and in 10% during the next 4 days. When diluted C alb cans suspensions were used the results were identical, but delayed 24 hours. There was no difference between various C. alb cans strains cultured from thrush lesions and other dermatoses. Embryos always died of C. albicans sepsis after infection of the chorioallantoic membranes. Reculture on artificial culture mediums and continuous passages were successfully done, and the histology of excision material from the cultures showed marked inflammatory infiltration n the mesodermal part of the allantois (HE tain) dense mycelia and numer ous cellular el ments (PAS stai) From the organs of dead embryos, C. lbicans could be recultured on artificial culture mediums in the same way as on chorioallantois and yolk. Intraperitoneal inoculation of white m ce showed re ults similar to those after infection of eggs of 9 intraperitoneally infected mice 6 died after 2 days and 3 after 3 days

Analogous experiments were made with yeast strains other than C. albicans. A to pathogenicity to chicken embryos

[8] (rch klin exper Dermat 203-543 397 1956.

and white mice there are marked differences between the strains e g C albicans is strongly pathogenic to chicken embryos and white mice The other yeast strains are apathogenic, except Sporobolomyces roseus which is apathogenic to chicken embryos but pathogenic to white mice.

Considering the frequent occurrence of C. albicans on human skin the authors recommend the chorioallantoic test for rapid preliminary differentiation of freshly isolated pure cultures of yeast strains This test permits a fast distinction between strains pathogenic and apathogenic respectively to chicken embryos A microscopic examination is suggested to exclude Cryptococcus neoformans which shows capsule formation but never mycelia

► [The procedure suggested here by Gotz, Nasemann and Sturde appears useful until simpler methods are developed for early differentiation between C. albicans and nonpathogenic yeastlike fungi. However a continued search is necessary for methods which do not require a complicated laboratory setup. What is needed is a readily available and suitable culture medium. Various "improved culture mediums which recently have been investigated by Rosenthal and Furnari at the New York Skin and Cancer Unit have failed to fulfil the claims made for them.—Eds.]

Investigation on Growth Stimulation of Candida Albicans by Antibiotics. Candida albicans infection of mucous membranes during or after antibiotic treatment of various infections has been clinically observed and bacteriologically confirmed in an increasing number of cases but unanimous explanation of this phenomenon has not yet been given J Meyer Rohn and Th. Lange-Brock[9] (Univ of Hamburg) therefore investigated the possibility of direct growth stimulation of C albicans by antibiotics using Warburg s manometric method This method was originally developed to determine the gaseous metabolism of living cells and has been used for some time in microbiology

Penicillin streptomycin chloramphenicol erythromycin bacitracin and particularly the tetracyclines were tested. In preliminary tests biotin which is known to possess growth stimulating effects (acceleration of proliferation) was also tested to assess the effectiveness of the Warburg method in in vitro experiments

... d only bacitracin and streptomy...
...se of biotin with markedly
...ans Penicillin effects were
... chloramphenicol minimal

(9) Arch. klin. u. exper Dermat 204 58 69 1957

only. With erythromycin, chlortetracycline and oxytetracycline, any positive influence on oxygen consumption of C. albicans was absent, i.e., no growth-stimulating effects were seen.

During protracted antibiotic treatment, vitamin deficiency symptoms were repeatedly observed and explained by the lowered resistance of mucosal membranes to C. albicans, antivitamin effects of antibiotics, prevention of vitamin synthesis by intestinal flora or reduced resorption of vitamins. Therefore, large doses of vitamin B complex during antibiotic therapy were recommended by many authors. However, in vitro experiments of other observers revealed growth stimulation of C. albicans by vitamin B. Again using Warburg's manometric method, the authors found vitamin B complex to have strongly stimulating effects on the growth of C. albicans, thus confirming the findings of others. *Consequently, vitamin B substitution during antibiotic treatment should be given parenterally to avoid the direct contact* of the vitamin with the pathologic gastrointestinal flora, which may be rich in C. albicans.

► [No significant progress appears to have been made on the problem of C. albicans superinfections and various other reactions to broad-spectrum antibiotics since this subject was discussed in the 1954-55 YEAR BOOK, pages 27-31.

Among the many hundreds of patients with acne, folliculitis, furunculosis, etc., treated for many months (even years) with daily oral doses of penicillin, chlortetracycline, oxytetracycline or tetracycline hydrochloride and with chloramphenicol and erythromycin for shorter periods, we have encountered relatively few in whom difficulties developed due to monilial cutaneous disease. Moreover, since we have prescribed mainly tetracycline there were almost none with *prolonged* gastrointestinal disturbances which could have been attributed to monilial overgrowth. This holds true even though one of us regularly prescribes a vitamin B complex (with B_{12}) preparation by mouth with the antibiotic, whereas the *other* does not! Thus, clinically, our patients under treatment with broad-spectrum antibiotics with or without vitamin B complex in general have shown no evidence of accelerated proliferation of C. albicans.

These events point out once again that great caution must be exerted when applying experimental laboratory findings to the clinical practice of medicine.—Eds.]

Growth of Candida Albicans on Keratin as Sole Source of Nitrogen. According to L. Kapica and F. Blank[1] (McGill U.), the pathogenicity of C. albicans for keratinized tissues has never been indisputably established. They investigated the keratinolytic activities of C. albicans by culturing the fungus on both human and animal keratin. Cattle hooves

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1) Dermatologica 115:81 293, August, 1957.

and white mice there are marked differences between the strains e g C albicans is strongly pathogenic to chicken embryos and white mice The other yeast strains are apathogenic except Sporobolomyces roseus, which is apathogenic to chicken embryos but pathogenic to white mice

Considering the frequent occurrence of C. albicans on human skin the authors recommend the chorioallantoic test for rapid preliminary differentiation of freshly isolated pure cultures of yeast strains. This test permits a fast distinction between strains pathogenic and apathogenic respectively to chicken embryos. A microscopic examination is suggested to exclude Cryptococcus neoformans which shows capsule formation but never mycelia.

► [The procedure suggested here by Götz, Nasemann and Sturde appears useful until simpler methods are developed for early differentiation between C. albicans and nonpathogenic yeastlike fungi. However a continued search is necessary for methods which do not require a complicated laboratory setup. What is needed is a readily available and suitable culture medium. Various "improved culture mediums which recently have been investigated by Rosenthal and Furnari at the New York Skin and Cancer Unit have failed to fulfil the claims made for them.—Eds.]

Investigation on Growth Stimulation of Candida Albicans by Antibiotics. Candida albicans infection of mucous membranes during or after antibiotic treatment of various infections has been clinically observed and bacteriologically confirmed *in an increasing number of cases, but unanimous* explanation of this phenomenon has not yet been given. J Meyer Rohn and Th Lange Brock[9] (Univ of Hamburg) therefore investigated the possibility of direct growth stimulation of C albicans by antibiotics using Warburg s manometric method. This method was originally developed to determine the gaseous metabolism of living cells and has been used for some time in microbiology

Penicillin streptomycin chloramphenicol erythromycin, bacitracin and particularly the tetracyclines were tested In preliminary tests biotin which is known to possess growth-stimulating effects (*acceleration of proliferation*) *was also* tested to assess the effectiveness of the Warburg method in in vitro experiments

Of all antibiotics examined only bacitracin and streptomycin showed effects similar to those of biotin with markedly accelerated proliferation of C albicans Penicillin effect were considerably weaker and tho e of chloramphenicol minimal

(9) Arch. klin. u. exper Dermat 204 38-69 1957

schenckii was limited to the skin and subcutaneous tissues. Diagnosis in each was readily established by routine culture technics. Response to iodides was prompt and complete. Stilbamidine and 2-hydroxystilbamidine also were effecti e and are considered the treatment of choice when there are disseminated lesions.

Bone and joint involvement is not rare in sporotrichosis it was present in 2 of the patients. Bone and joint involvement may result from direct extension of cutaneous or subcutaneous lesions or from spread via the blood stream. The latter is the more common mode of infection. The organism may be seeded into the synovium with resultant spread to adjacent cartilage and bone or into the medullary region of bone directly Lesions often are multiple and usually lytic and destructiv i their radiologic appearance. Roentgenologically the lesio s often are confused with tuberculosis although they may also resemble metastatic neoplasm destructiv rheumatoid arthritis or other conditions.

One of the patients had hematogenous dissemination of the organism with widesp ead involvement of the skin and ar ticular t ssues. The ski lesions responded satisfactorily to iodide therapy but articular involvement persisted and progressed despite continued therapy over 16 years. The other patient with systemic lesions had no h story of cutaneous lesions. Initially diagnosis was confused with rheumatoid arthritis. Eventually a draining sinus formed in the right popliteal region. The disease of the joints progressed and ystemic symptoms appeared. Diagnosis of sporotrichosis of the joints was established by culture of the rganism in material from the left elbow Later fulminating staphylococcic septicemia led to the patient s death.

North American Blastomycosis. Arthur C Curtis and Florante C Bocobo[3] (Univ of M chigan) review present day knowledge concerning this disease. The precise mode of infection is not fully known It generally is presumed to be exogenous w th the infective saprophytic form of the or gani m existing in nature. The soil is trongly suspected as the natural reservoir of the organism Blastomyces derma t tidis although occurrence of natural infection in dogs and horses suggests that animals may serve as reservoirs. Open k n lesions and body secretions or exudates teem with the

(3) J Chronic Dis 5 444-459 April, 1957

and human nail cuttings were used as the sole source of nitrogen. It was found that C albicans can grow on mediums containing keratin salts and glucose or keratin and glucose. Glucose is necessary to initiate growth Of 3 glucose concentrations tested (2 4 and 8%) the best results were obtained with 2% glucose.

The appearance of nitrogenous breakdown products of keratin in culture mediums was followed for 4 months qualitatively by ninhydrin tests and paper chromatography and quantitatively by determination of total nitrogen and alpha amino nitrogen The first amino acids appeared in the culture liquid 40 days after inoculation Some of the spots on the chromatograms have not yet been identified but it is evident that almost every amino acid so far detected in keratin hydrolysates also appears under the conditions of the present experiments The total nitrogen increased during the course of study and was found to contain only a small proportion of free amino acids thereby proving that C. albicans can digest keratin Candida albicans did not develop more than a negligible initial growth in a medium to which no nitrogen was added.

Although this purely chemical investigation cannot provide a complete answer to the question of pathogenicity its results strongly indicate the pathogenicity of C. albicans for keratinized tissues Further the relation between sugar metabolism and keratinolytic activities of C albicans corroborates and explains many clinical observations relating cutaneous moniliasis to the sugar content of the keratinized tissues

► [Knowledge such as this concerning the biochemistry of the growth and survival of fungi may well lead to new therapeutic approaches. It may prove more feasible to interfere with the metabolism and growth of dermatophytes by altering the substrate than by attacking the fungi themselves —Eds.]

Sporotrichosis Report of 12 Cases, Including Two with Skeletal Involvement, is presented by W M Mikkelsen R. L. Brandt and E. R. Harrell[2] (Univ of Michigan) Sporotrichosis usually is limited to the skin and subcutaneous tissue but extracutaneous dissemination may occur Infection is generally the result of inoculation of an injured area of skin although such history often is lacking in systemic forms In 10 of the 12 patients observed infection with Sporotrichum

(2) Am. Int Med. 47 435-439 September 1957

treated with the newer chemotherapeutic agents. Remarkable improvement and apparent cures have been attained in a significant number of cases of systemic blastomycosis by treatment with stilbamidine and 2-hydroxystilbamidine, but they do not control the disease in all patients. Toxic neuropathy has appeared in 50-60% of reported cases under stilbamidine treatment.

Management of pulmonary blastomycosis today is comparable to that of pulmonary tuberculosis, in which surgical intervention has become a valuable adjunct to chemotherapy. Pulmonary resection is used when a localized pulmonary focus exists without evidence of dissemination and for the residual, irreparably damaged tissues after chemotherapy.

Cryptococcosis with Cutaneous Manifestations: Four Cases with Review of Published Reports are presented by Morris Moore (Washington Univ.). One of the patients had an ulcerated patch over the right pectoral region, 1 had subcutaneous abscess with surgically induced sinus and 1 had a group of erythematous, subcutaneous nodules shortly before death. The 4th case is described here.

Woman, 35, had acneform, crusted, irregular lesions on the arms, thighs and back, some wet, deep and erythematous and capped with plugs that on removal revealed central cores. Some of the lesions were cultured and Cryptococcus neoformans was isolated. Treatment with sulfadiazine, Acti-dione and potassium iodide was started. X-ray therapy 75 r was given weekly for 7 weeks to each of 4 lesions: granulomatous, raised, crusted lesions on the back of the neck (Fig. 51), granulomatous lesion with satellites on the right shoulder (Fig. 52), deep nodular erythematous lesion on the left anterior thigh (Fig. 53) and punched out, crusted lesion on the posterior thigh (Fig. 54).

Acti-dione was discontinued after about 2 months. The lesions began to disappear and after another 2 months, biopsy and culture of scal[p] plaque were negative. However during the next few months several new lesions appeared and culture revealed C. neoformans. Nystatin was given, 500,000 units daily for 5 days and sulfadiazine treatment was continued. The skin cleared temporarily but 1 month later headache, stiff neck and sore throat developed. Cerebrospinal fluid cultures revealed C. neoformans. Despite treatment, including fever therapy, the course was downhill and the patient died after about 6 weeks. Autopsy revealed generalized cryptococcosis.

Cryptococcosis presents a varied clinical picture and often mimics other diseases. Clinical diagnosis is practically impossible. Cutaneous lesions also are varied and include pap-

J. Invest. Dermat. 28:159-182, February 1957.

tissue forms of the organism and provide excellent opportunities for contagion yet no direct natural transmission from man to man has been proved The skin and lungs are looked on as the most probable entry for the infection Recent studies suggest that most of the skin lesions are secondary to a healed or undiscovered primary focus in the lungs. This concept is gaining many proponents including the present authors.

There is no definite diagnostic pattern in the clinical history and manifestations. Even the typical cutaneous granuloma is only suggestive Clinical diagnosis based on history and physical observations is at most presumptive and made unequivocal only by positive demonstration and identification of the causative organism in the laboratory When the tissue phase of B dermatitidis is recognized in fresh or stained specimens it is wise to confirm this by isolation and identification of the organism in cultures.

Cutaneous hypersensitiveness in a patient with blastomycosis is shown by skin test, using a vaccine of the killed organisms or culture filtrate called blastomycin. A positive test generally indicates past or present infection but is of only presumptive diagnostic value. An important misleading factor is occurrence of cross reactions with histoplasmin and coccidioidin and the antigen of B brasiliensis. The serums of patients with blastomycosis are able to fix complement with suspensions or extracts of B dermatitidis as antigens. This test also has only presumptive value

In untreated patients prognosis of the classic cutaneous blastomycosis is good as regards life expectancy but its chronic recurrent course extends through many years Conversion into the systemic form fortunately is rare In evaluation of prognosis in the systemic disease much help can be obtained from study of the patient s immunologic picture Favorable outcome generally is expected in patients with negative complement fixation test and positive skin test. However high titer of complement fixing antibodies and negative skin reaction (indicating anergy) usually means grave prognosis

In cutaneous blastomycosis best therapeutic results are obtained through a combination of iodide treatment surgical procedures roentgen therapy and vaccine hyposensitization. Lesions recalcitrant to these regimens should be

rganism 5-20 μ in diameter and surrounded by a thick refractile, gelatinous capsule.

Review of the literature revealed 36 cases with cutaneous manifestations, representing about 15% of total reported cases. The lungs probably are the primary focus of infection from which the organisms spread hematogenously to in olve the cerebrospinal system and skin. In some patients systemic involvement may be dormant. Subsequent disturbance of the skin such as trauma, may be responsible for initiation of a cutaneous lesion through hematogenous dissemination.

Co-existence of lymphoma or lymphoblastoma with cryptococcosis has been known for some time It is possible that the debil tating effect of the lymphoma on the tissue is suffi cient to lower tissue resistance to infection with C neoformans or to allow a dormant lesion to be reactivated. There also is evidence that cortisone and ACTH may hasten spread and intensity of cryptococcosis.

N specific agent for treating cryptococcosis is known. Potassium iodide and x-ray therapy have proved of value in some cases, but not in others The sulfonamides have been beneficial in clearing cutaneous lesions but they do not inh bit ystemic spread. Fever therapy has been suggested but is hazardous in patients with brain lesions.

► [The original article contains thorough review of the subject —Eds.]

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7 OTHER INFECTIONS INFESTATIONS

Epidemiology of Herpetic Infections is reviewed by T F M Na Scott[4] (Uni of Pennsylvania) The host reaction to nfection may be severe leading to clin cal manifestations or mild and bcl nical. Recognition of the clinical picture follow ng infection may be difficult because the manifesta tion are protean l p to the present it is possible to ecog lesions of the sk in the form of herpes simplex, eczema herpeticum and traumatic herpes of the mucous membranes a c te gingivostomatitis vulvovaginitis and herpes progen talis of the eye as keratoconjunctivitis of the central nervous system as encephalitis as a generalized ll ess, in

4 Am J Ophth 43 14 47 September 1954.

ules pustules with or without crusts nodules that may be erythematous superficial or subcutaneous, superficial plaques acneform lesions granulomas, superficial and deep ulcers verrucous or papillomatous forms vegetative types gummatous lesions ecthymatous and ecchymotic lesions, and subcutaneous abscesses with or without sinus forma



Fig 51 (top left) —Crusted, ulcerated lesion on back of neck of patient with cryptococcosis.
Fig 52 (top right) —Erythematous and scaly nodules on back.
Fig 53 (bottom left) —Irregular erythematous plaque on thigh.
Fig 54 (bottom right) —Crusted, erythematous nodule on thigh.
(Courtesy of Moore, M J Invest Derm 28 159-182 February 1957)

tion. The histologic picture varies depending on the type of lesion examined, but diagnosis is relatively easy when organisms are demonstrable The organism causing the disease is actually a single species C neoformans although confusion regarding its taxonomy has resulted in many syno-
other
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(4) Am J Obst. 43 134 47 September 1954.

adults resembling grippe infectious mononucleosis, or smallpox and in newborn infants in whom fatal involvement of the brain lungs adrenals and liver may occur

The reaction to herpetic infection may be so mild that it is recognizable only by laboratory methods, which fall into two categories—isolation of the virus and measurement of antibodies There are 3 recognized antibodies measured at present neutralizing complement fixing and skin test. In primary infection with herpes virus the organism is readily isolated from the area involved Antibody levels persist for a variable time. In childhood, a single primary infection may not allow the virus to establish itself and repeated subclinical infections may have to occur until a balance is achieved and the host maintains a constant level of antibody

Although the virus can also be isolated from the lesions in recurrent infections the antibody response is different. For the most part it appears that circulating antibody is present at the time of the attack and does not alter after the attack. While this absence of reaction is probably the usual situation it has been shown that some adults react to a recurrent attack by rise in antibodies either neutralizing complement fixing or both

As incidence of subclinical infection by the herpes virus is much greater than that of the clinical absence of history of a primary illness is not of great value in determining the incidence of susceptibles. This must be done by measuring the presence of antibodies in the population at large. For survey purposes the complement fixation test is the most satisfactory one being cheaper and quicker than the neutralization test and paralleling it closely in sensitivity The skin test is not reliable for survey purposes because in persons over age 50 there is a decrease in incidence of positive skin tests despite the presence of complement fixation and neutralization antibodies and in infancy skin tests are notoriously unreliable In older childhood and young adulthood, there is excellent parallelism among the 3 tests

Surveys have indicated that herpetic infections are commoner in the lower income groups The greatest incidence of susceptibles is between age 6 and 24 months By the 5th year incidence of infections reaches that of the adult population.

It is clear that the herpes virus must be acquired by a susceptible host from another person carrying the virus. Several

studies have indicated that a history of contact with a known case of herpetic infection is relatively uncommon. This means that the virus is carried by persons without clinical manifestations. These carriers fall into two groups, those that carry the infectious agent for a period immediately following the acute disease even though clinically recovered and those in whom the virus appears without reference to preceding or accompanying clinical manifestations.

The incubation period has been difficult to estimate because of the ubiquitous nature of the virus but it appears to be relatively short, probably usually between 3 and 9 days. The virus has been isolated from the stools and saliva of carriers and patients with clinical disease. It probably appears in the stool as a result of swallowing but actual infection of the alimentary tract below the mouth is possible. Presumably close physical contact is required for spread of the virus. Early infancy is a period of life during which close bodily contact is part of everyday life. The infrequent primary infection of the adult can usually also be traced to physical contact, e.g. from kissing which leads to an attack of stomatitis, or sexual intercourse, during which the male with herpes progenitalis may give rise to primary vulvovaginitis in the female.

It seems that a trigger mechanism may be involved in determining whether clinical or subclinical infection may occur. Teething in the infant leads to traumatized gums which might form the point of entrance of the virus. Infection of the skin is almost always due to inoculation of virus directly on to traumatized areas.

Certain changes in the physiology of the patient are important in the epidemiology of recurrent herpes. These precipitating factors include fever, menstruation, emotion, nerve injury, sunburn and irritation from cold winds.

▶ [An interesting and informative article. In herpes simplex infection superimposed on atopic dermatitis, especially in children, it is not uncommon that a definite history of exposure to a family member with acute herpes simplex can be elicited. Unfortunately the advances in our knowledge of skin-test reactivity and antibody titers have not been matched by similar progress in finding specific preventive therapy for herpes simplex. —Eds.]

Kaposi's Varicelliform Eruption. George B. Sexton (London, Ont.), Nicholas A. Labzoffsky and William G. Poss (Toronto) *report* 2 cases in adults with atopic dermatitis.

(10) A.M.A. Arch. Dermat. 75:341-347, March, 1957.

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peticum which occurred in a ward for treatment of skin disease.

Boy aged 9 months was hospitalized for eczema, superimposed on napkin erythema, present since age 3 months. There were weeping and crusted eczematous lesions on the trunk, face and limbs, with enlargement of the lymph nodes but without obvious signs of secondary pyogenic infection. H was treated with saline baths and cooling lotions and for time the skin lesions improved considerably A relapse occurred, and 50 mg cortisone/day was given for 3 days, without ef fect. Later the skin eruption cleared except for some lesions on the face.

While he was still on the ward, 2 other children w th infected ec zema were admitted, and the possibility that they had herpes simplex infection was considered. The virus was isolated from the skin of 1 patient. All patients on the ward were given gamma globulin as a prophylactic The patient recei ed 6 ml. intramuscularly (500 mg) The following day typical herpetic eruption appeared on the face, back and legs. The white blood cell count was 15,500, and coagulase positive staphylococci and Streptococcus hemolyticus were cultured from the skin lesions. Antibiotic treatment was started, and a further dose of gamma globulin (500 mg) was given. Diagnosis of Kaposi s varicelliform eruption was confirmed by the finding of multinucleate epithelial cells in the vesicular lesions. After slow improvement there was sudden deterioration and collapse, with dyspnea, a distended abdomen and signs of severe shock until death. At autopsy many necrotic lesions were discovered in both adrenals, and herpes simplex virus as recovered from the adrenals, skin, brain, lymph nodes and uvula.

Children with eczema, particularly extremely young ch l dren, are so usceptible to herpetic infection that it seems ad isable to use every means to reduce risk of exposure and subsequent infection. Source of infection is of greatest im portance and as efforts are made to avoid bringing eczema tous children into contact with vaccinia virus by postponing vaccination, so should risk of exposure to herpes virus be minimized. It is probably advisable to egard all patients with infected eczema as potentially infected with herpes viru unless pro ed otherwise, especially wh le laboratory test are being made or if res lts are equivocal.

The ncubation period of herpes is 4-7 days, but by the time the first dose of gamma globulin was given to the pa tient virus multiplication was almost certainly well advanced At this stage the viru would be largely intracellular and thus beyond the reach of ant body Gamma globulin which contains herpes-neutralizing ant body should prevent infection if given before or immediately after exposure. De

The first ended fatally and specialized animal laboratory studies or autopsy findings were not obtainable. A viral agent isolated from the cutaneous lesions of the other was identified as belonging to the variola vaccinia group.

The virus possessed some of the characteristics which pertain more to variola than vaccinia and some which are inherent in vaccinia virus. Its pathogenicity for rabbits by any of the usual routes and inability to propagate serially in mouse brain puts it in closer relation to variola than to vaccinia but its resemblance to vaccinia is manifested by high pathogenicity for chick embryo and by the fact that lesions produced on the chorioallantois were indistinguishable from those produced by vaccinia virus. The authors conclude that the agent cannot be classified as true vaccinia or true variola but is a variant of one of these viruses. Since variola is uncommon in Canada it is probable that the virus is a variant of vaccinia especially since the patient had contact with a recently vaccinated son.

Review of the literature reveals a diversity of opinion as to the etiologic agent in Kaposi's varicelliform eruption. Available evidence indicates that at least two viruses, vaccinia or herpes simplex, may be the causative agent. That the condition may be produced by the virus of herpes simplex has been conclusively demonstrated repeatedly. The evidence that true vaccinia virus may be responsible is not convincing since in no instance were detailed studies of comparison of the isolated virus with that of vaccinia carried out. The conclusions were based on serologic cross reaction or on histologic picture of the lesions. It is probable that many cases that have been reported as caused by the vaccinia virus were actually infected with a variant of vaccinia, as in the authors case.

► [There are enough cases of generalized eruptions in atopic persons following vaccinia vaccination or exposure to persons vaccinated with vaccinia virus to justify considering their involvement to be the result of a vaccinia virus infection. Some years ago it was suggested that the name Kaposi's varicelliform eruption be abandoned and replaced by a name indicating both the specific virus causing the superimposed infection and the underlying disease such as, e.g. disseminated cutaneous vaccinia virus infection, superimposed on atopic dermatitis. —Eds.]

Adrenal Necrosis in Generalized Herpes Simplex. R. T. Brain, R. C. B. Pugh and J. A. Dudgeon[7] (London) report a case of fatal Kaposi's varicelliform eruption or eczema her

(7) Arch. Dis. Childhood 32: 120-126, April, 195

petiginum which occurred in a ward for treatment of skin disease.

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The incubation period of herpes is 4-7 days, but by the time the first dose of gamma globulin was given to the patient, virus multiplication was almost certainly well advanced. At this tage the virus would be largely intracellular and thus beyond the reach f antibody Gamma globul n which contains herpes-neutralizing antibody should prevent infection if gi en before or mmediately after exposure. De

pending on the circumstances and age of the child, passive immunization with gamma globulin should be considered for patients with infantile eczema on hospitalization A reasonable dosage would be 0 1 ml./lb body weight with a further similar dose 4-6 weeks later if hospitalization is likely to be prolonged The chances of sensitization from repeated injections of gamma globulin are negligible

Fatal Agammaglobulinemic Progressive Vaccinia Report of Case with Classification of Human Cutaneous Vaccinia is presented by Henry M Lewis and F Craig Johnson[8] (Children s Hosp Denver)

Negro girl vaccinated 8½ months after birth, 3 weeks later showed

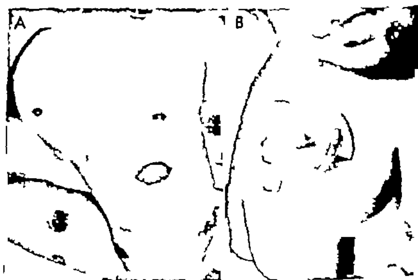


Fig 55 — Appearance of patient on admission, 25 days after vaccination. Note lesions in all stages of development with no attempt at healing. A, right lower extremity. B, site of vaccination and perineal area. (Courtesy of Lewis, H. M. and Johnson, F. C. A.M.A. Arch Dermat 75 837-844 June, 195)

multiple lesions of vaccinia in all stages of development on the face trunk and extremities (Fig 55) They simulated a primary vaccinia reaction in every respect and showed no evidence of attempted healing Electrophoretic analysis of serum proteins revealed complete absence of gamma globulin. Complement fixation test against vaccinia virus was positive 1:4 hemagglutination inhibition test was positive 1:5 no virus neutralizing antibody was demonstrable The patient s condition deteriorated rapidly despite treatment with vaccinia immune gamma globulin, poliomyelitis immune gamma globulin, transfusions and ACTH She died 38 days after vaccination.

At least three different types of measurable antibodies de-

(8) A.M.A. Arch. Dermat. 75:837-844 June 1957

velop within 10 days after vaccination. Review of the antibody titers in the authors patient show that she was able to manufacture small amounts of hemagglutination inhibition antibody but complement-fixing antibody production was inconsequential and there was no endogenous virus-neutralizing antibody It is the consensus of virologists that neutralizing antibodies are the most important immunologically

The poor antibody response is presumably due to agammaglobulinemia, but most agammaglobulinemic children despite inability to form humoral antibodies, undergo a normal vaccinia reaction. Moreover the presence of gamma globulin in adequate amounts may not guarantee adequate antibody production Patients in whom no antibodies are formed despite quantitatively normal gamma globulin levels may have dysgammaglobulinemic progressive vaccinia a disorder which is amenable to treatment with hyperimmune vaccinia gamma globulin.

The discovery of the properdin system may cast some light on these perplexing immunologic phenomena. This is an independent defense system present in normal human serum which destroys bacteria, inactivates viruses kills protozoa and lyses abnormal erythrocytes Properdin is a euglobulin nonspecific in action and present in the serum of mammals without previous antigenic stimulation. Bacteria are attacked by it immediately several days before specific antibodies are formed. Thus, it constitutes the first line of defense against invading organisms.

The authors offer a classification of human cutaneous vaccinia based on recent developments in the field of immunology Local reactions include primary vaccinia and accelerated reactions. Secondary inoculation reactions include satellite vaccinia and eczema vaccinatum Generalized reactions due to hematogenous dissemination of vaccinia virus are progressive vaccinia and generalized vaccinia. Generalized reactions due to hypersensitivity to vaccinal proteins include roseola vaccinosa, erythema multiforme and urticaria.

[In patients with disseminated symmetrically distributed vaccinia virus infection superimposed on atopic dermatitis, it would be difficult to differentiate between eczema vaccinatum and generalized vaccinia. We know of no proof that in the former the distribution of the virus is exclusively or even largely by contact and not by hematogenous distribution.—Eds.]

Motor Complications of Herpes Zoster David Kendall*

(*) Brit M J 2 16-618, Sept 14, 1957

pending on the circumstances and age of the child, passive immunization with gamma globulin should be considered for patients with infantile eczema on hospitalization. A reasonable dosage would be 0.1 ml./lb. body weight with a further similar dose 4-6 weeks later if hospitalization is likely to be prolonged. The chances of sensitization from repeated injections of gamma globulin are negligible.

Fatal Agammaglobulinemic Progressive Vaccinia: Report of Case with Classification of Human Cutaneous Vaccinia is presented by Henry M. Lewis and F. Craig Johnson[8] (Children's Hosp., Denver).

Negro girl, vaccinated 8½ months after birth, 3 weeks later showed

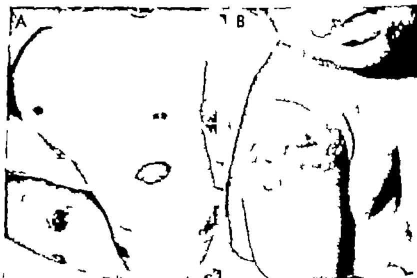


Fig. 55. Appearance of patient on admission, 25 days after vaccination. Note lesions in all stages of development with no attempt at healing. *A*, right lower extremity. *B*, site of vaccination and perineal area. (Courtesy of Lewis, H. M., and Johnson, F. C.: A.M.A. Arch. Dermat. 75:837-844, June, 1957.)

multiple lesions of vaccinia in all stages of development on the face, trunk and extremities (Fig. 55). They simulated a primary vaccinia reaction in every respect and showed no evidence of attempted healing. Electrophoretic analysis of serum proteins revealed complete absence of gamma globulin. Complement fixation test against vaccinia virus was positive 1:4, hemagglutination inhibition test was positive 1:5, no virus-neutralizing antibody was demonstrable. The patient's condition deteriorated rapidly despite treatment with vaccinia-immune gamma globulin, poliomyelitis-immune gamma globulin, transfusions and ACTH. She died 38 days after vaccination.

At least three different types of measurable antibodies de-

(8) A.M.A. Arch. Dermat. 75:837-844, June, 1957.

elop within 10 days after vaccination. Review of the antibody titers in the authors patient show that she was able to manufacture small amounts of hemagglutination inhibition antibody but complement fixing ant body production was inconsequential and there was no endogenous virus neutralizing antibody It is the consensus of virologist that neutralizing antibodies are the most important immunologically

The poor antibody response is presumably due to agammaglobulinemia, but most agammaglobul nemic children despite inability to form humoral antibodies undergo a normal vaccinia reaction Moreover the presence of gamma globulin in adequate amounts may not guarantee adequate antibody production. Patients in whom no antibodies are formed despite quantitat vely normal gamma globulin levels may ha e dysgammaglobulinemic progres ve vaccinia, a d sorder which is amenable to treatment with hyperimmune vaccinia gamma globulin.

The discovery of the properdin system may cast some l ght on these perplexing immunologic phenomena. This is an n dependent defense system present in normal human serum which destroys bacteria, inactivates viruses, kills protozoa and lyses abnormal erythrocytes Properd n is a euglobulin nonspecific in action and present in the serum of mammal without previous ant gen c stimulation. Bacteria are attacked by t mmediately several days before specific antibodies ar formed. Thus t constitutes the first line of defense against in ading organisms.

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Motor Complications of Herpes Zoster David Kendall[9]

(9) Brit M J 2 4418, Sept 14, 1957

reports 14 cases of herpes zoster in which paralysis resulted from the infection That the anatomic relations of the eruption and the paralysis were not constant and often did not coincide strongly supports the contention that herpes is essentially a disease of the spinal cord or brain stem and not a radicular disorder as was originally supposed. As complement fixation tests for herpes have been positive in a proportion of cases of Bell s palsy it is suggested that some of these cases may be due to herpes zoster In this connection, occasional occurrence of severe pain in the mastoid and upper cervical region before paralysis may be significant.

The pattern of history and clinical findings in cases of neuralgic amyotrophy follows closely that of herpetic paralysis in the upper extremities, except for absence of the eruption. It seems likely that neuralgic amyotrophy may in some cases at least result from infection with herpes zoster virus. In general, motor weakness or paralysis is not an uncommon accompaniment of herpes zoster Recovery of paralyzed extremities is usually nearly complete, but incidence of recovery of facial paralysis is not as satisfactory as in true Bell s palsy

Visceral Lesions in Herpes Zoster Unmyelinated afferent nerve fibers with their cell bodies in the posterior root ganglions run from the viscera uninterruptedly through the autonomic ganglions and white rami communicantes to enter the posterior nerve roots with those from somatic tissues It might be expected therefore that irritation of the unmyelinated afferent fibers in the posterior nerve roots or peripheral nerves, or their cell bodies in the posterior root ganglions would produce changes not only in the skin and somatic tissues but also in the viscera. The literature on herpes zoster contains a number of descriptions of localized visceral disturbances accompanying the skin lesions

R Wyburn Mason[1] who has often observed this association reports 8 cases. The visceral disturbance occurred particularly in those viscera or parts of viscera supplied with afferent fibers by the posterior nerve roots corresponding to the zonal areas affected. As in the skin and deep tissues, the effects are vasodilatation edema hemorrhages inflammatory changes and predisposition to vascular thromboses The affected gut shows hypermotility and spasm

CASE 1—Man, 42, with typical lesions of herpes zoster on right

(1) Brit. M J 1 678 681, M 23 1957

shoulder and front, back and right side of the lower neck, showed cough and hoarseness 3 day after appearance of skin lesions. Laryngoscopy disclosed redness and edema of the right ocal cord. Bronchoscopy revealed edema and redness strictly limited to the right side of the tracheal mucosa. With fading of the skin lesions cough and hoarseness gradually ceased.

CASE 6.—Woman, 60 with skin lesion of herpes zoster on the left side of the lower bdomen, loin and back showed sudden severe frequency and burning micturition on the 12th day after onset of the cutaneous eruption on the 14th day hematuria occurred. She was severely constipated. Cystoscopy revealed marked redness and edema of the bladder fundus, chiefly on the left side. Barium enema disclosed spasm of the ascending and transverse colon nd dilatation of the descending colon. With healing of the skin lesions, urinary symptoms and constipation gradually diminished though both these and pain persisted during the next 6 months.

[Several reports in recent year have stressed the occurrence of internal involvement in herpes zoster. This may help to explain the extreme feeling of malaise and of generally being sick in some middle-aged and older patients ith herpes zoster.—Eds.]

Herpes Zoster with Liver Damage is reported in 7 patients by W Siede[2] (Darmstadt, Germany) In none was there a history of previous liver or gallbladder disease. Signs and symptoms pointing to possible liver disease occurred imultaneously with, shortly after or before appearance of herpes zoster a d consisted of malaise loss of appetite, feel ng of pressure pains in the liver region and diarrhea. The liver was enlarged and firm the spleen was palpable occasionally Icterus was clearly marked in 1 and subicterus in 3 patients Liver function tests were positi e during the acute stage Serum electrophoresis how ed albumin and globul n values corresponding to those found n patients with liver damage. A hemogram revealed cell types found in herpes zoster and in irus hepatitis (nrocytes) Liver biopsy done in 2 cases showed hepatitis. The periportal tissue was increased and showed chronic nflammatory nfiltration the number of Kupffer cells was increased within the hepatic lobules and the liver cells exhibited a granular or vacuolar cytoplasm oc casionally dist nct cell membranes and a synthesis of nuclei In 5 patients, th hepatitis disappeared with n a few weeks, in 1 it showed very slow improvement after 8 months and in another it persisted after 2 years.

The concurrence of herpes zoster and hepatitis is rather rar and may be explained by assuming that a hepatotropic zoster virus a neutrotropic hepatitis virus (in cases n which

(2) Deutsche med Wchnschr 81 1461 1462, August, 1956.

hepatitis preceded the zoster eruption) or one and the same virus caused the cutaneous and hepatic involvement.

Transitory Neurologic Complications of Varicella. John L. Simon (Nanuet N Y) Sidney W Berezin (Spring Valley N Y) and Alan J Maged[3] (Suffern N Y) report 2 cases.

CASE 1.—Girl 2½, during the course of chickenpox, suddenly began to fall to the right whenever she attempted to walk. Neurologic examination was negative except for a disturbance in balance. It was the opinion of the neurologist that the disequilibrium was of vestibular origin. The parents recalled that the child had complained of a sensation about her right ear earlier in the day confirming the opinion that the symptom had a peripheral source. The clinical picture had apparently resulted from transitory edema of the labyrinth. Recovery was rapid, and there were no sequelae.

CASE 2.—Boy 7 returned to school after what seemed to be an uncomplicated attack of varicella. The next day he had pains in his legs and the following day he had posterior headache and saw spots before his eyes. He could not walk and screamed when urged to try The temperature was normal neck slightly stiff and reflexes were normal There was exquisite muscle tenderness in both legs. The following day the child had visual hallucinations and still could not walk. White blood cell count was 12,800 Two days later the conspicuous findings included weakness of the muscles of the back with the tripod sign." The neck was stiff the left leg was still weak and tender but the right had improved. A spinal fluid specimen was clear and colorless there were 4 cells/cu. mm., all mononuclears, and protein content was 34 mg./100 cc. Immediately after the lumbar puncture the patient said he could walk. By evening the gait was almost normal and there was no neck stiffness. There was no muscle tenderness and only minimal weakness of the left lower extremity The child subsequently went on to recovery

The presence of hallucinations in this case indicates cerebral involvement. The inability to walk was probably of spinal origin The headache neck stiffness and leg pain point to involvement of the meninges and nerve roots. The occurrence of diffuse involvement of the nervous system shortly after chickenpox makes the diagnosis of varicella encephalomyelitis almost mandatory The rapid recovery is not exceptional This complication of chickenpox is quite rare.

Light and Electron Microscopic Studies on Morphology of Molluscum Contagiosum Virus and Its Inclusion Body Formations and on the Clinical Course Serology Histopathology and Pathogenesis of Molluscum Contagiosum.—
I History and clinical course are described by Th Nasemann[4] (Univ of Munich) Molluscum contagiosum is a wart

(3) New York J. Med. 57 3182-3183 Oct 1 1957
(4) Hautarzt 8:301-309 July 1957

like epitheliosis, an infectious acanthoma, caused by a virus and showing analogies with other virus diseases of the skin and of the eye. Acanthosis is also seen in verruca vulgaris nd condyloma acuminatum. Cytoplasmic inclusions were also found in variola vaccinia, inclusion blenorrhea, tra choma, etc molluscum virus and trachoma virus cause local chronic, infectious processes

Clinical examination of 34 patients with molluscum con tagiosum produced data referring to morphology and num ber of lesions (up to 400 in a girl aged 8) localization (face neck, eyelids genitals, axillae are usually involved palms and soles rarely) age incidence (average 12 years) sex inci dence (f 34 patients, 20 were females) frequency of occur rence (1% of skin cases) seasonal nfluence (high incidence during cold months, with a peak in March) and contributing factors (poor unhygienic conditions may be a factor)

Differential diagnosis may be difficult in atypical cases e g molluscum contagiosum giganteum. In patients with the tumor like form of the disease epithelioma and sarcoma have to be excluded and molluscum contagiosum of eyel ds mu t be differentiated from syringocystadenoma Molluscum con tagiosum of the palpebral margin, conjunctiva or cornea may cause conjunctivitis, keratoconjunctivitis, keratitis and for mation of phlyctenae in which case trachoma and follicular conjunctivitis have to be excluded. Secondary infections may change the linical appearance but often cause spontaneous healing

Prognosis is good Occasionally regional lymphadenopa thy was bserved in this series. Healing with formation of hypertrophic scars is rare In treatment, superficial al tting followed by expression of the pulpy contents, application of tincture of iodine and dressing with Aureomycin® produce satisfactory result

IV Histochemistry ultrahistology pathogenesis and mor phology of the molluscum ontagiosum virus are discussed by Nasemann[8] It has been observed that the inclusion bodies give a positiv Feulgen reaction The intensity of red stain ing parallels th maturing process. While in the lower layers of the stratum spinosum the cells contain only a few Feul gen-positive granules in th top layers the cells are packed w th them.

( ) Hautarzt 8 443-438 October 1957

The behavior of the molluscum contagiosum tissues in sulfhydryl staining and the McManus reaction implies that the keratinization in this disease follows the same pattern, though with increased intensity, as in the normal epidermis. It is assumed that in the inclusion bodies keratinization begins on the periphery and proceeds by layers.

Electron microscopic studies have shown that occasional specimens of molluscum contagiosum contain, besides square elementary bodies, also fibers with periodic structure which are very similar to collagen fibers. Since the periodic structure of collagen, nerve fibers and of ribonucleoprotein is very similar, it has been speculated that the fibers seen in molluscum contagiosum might represent ribonucleic acid fragments.

Electron microscopic studies have also revealed that in the cells of the stratum spinosum which did not yet present inclusion bodies the cytoplasm contained varying amounts of viral elementary bodies which were not surrounded by a membrane and were fewer in number than within the mature inclusion bodies. The mature elementary bodies in the fully developed inclusion bodies appeared ovoid and measured 210×360 mμ. These measurements agree with the size of the elementary bodies obtained from ground molluscum tissue suspensions.

The author found that when smear preparations from molluscum nodule pulp suspension were exposed to pepsin or trypsin these did not affect the inclusion bodies. Furthermore it was found that the rete cells may contain elementary bodies without the presence of inclusion bodies in the same cell. The great number of elementary bodies in the molluscum pulp preparation may be explained by the assumption that some of the mature inclusion bodies burst and free the elementary bodies. The bursting cells necessarily leave cell membranes behind. Thus a molluscum pulp preparation may show a great variety of tissue elements: intact basal cells, rete cells with a few elementary bodies in the cytoplasm, cells with enlarging inclusion bodies, bursting inclusion bodies, free elementary bodies, empty cell membranes and membrane fragments.

The molluscum contagiosum virus reacts to pepsin hydrolysis the same way as the vaccinia virus. In smear preparations the molluscum viruses aggregate in a typical pattern

► [Usually the diagnosis of molluscum contagiosum is among the easiest to make, but if not kept in mind it can be easily overlooked. We have seen cases in which it was difficult clinically to make a differential diagnosis between molluscum contagiosum and basal cell epithelioma or keratoacanthoma.—Eds.]

Contribution to Morphogenetic and Histochemical Knowledge on Molluscum Contagiosum. J Gay Prieto A P Rodriguez Perez and G Jaqueti[6] (Madrid) record a number of findings differing from the generally accepted ideas concerning the morphogenesi and histochemical structure of this condition. Besides the u ual eosin-hematoxylin, van Gieson and f chsin-resorcin stains they used the methyl green-pyronine technic and McManus-Lill e Hotchkiss and supplementary tains

The histologic changes in the epithelium of the molluscum body do not begin as is generally accepted, by the appearance of perinuclea vacuoles that continue to grow within the cytoplasm but by vacuoles that are intranuclear and whose growth leads to the appearance of globular corpuscles that displace the cytopla m At times only one vacuole ppears, at other times two or more They tend to increase the ize f the nucleus and make it esicular In some cases the chromatin appears almost completely d splaced toward the membrane, but more frequently it appears in a reticular pattern, with fine trabeculae which delim t clear globular spaces. Occasionally a large chromatin body remains u ually eccentrically placed. At times however the residual chromatin material remains in the center of the nucleus, giving the impression of a perinuclear vacuole

The alleged hem cal changes of the thymo- and ribonucleic cids a believed to be merely false mages. In reality it is the hemical material of the nucleus that by growth of the inclusion bodies adopts a spongy texture. Around the growing epithelial corpuscles f the molluscum there is a capsule composed of mucopolysaccharides, poss bly a residue of those existing in the nterstices. In the free corpuscle al eady matured the capsule can hardly be discerned and often is completely lacking

The uthors could not demonstrat by histochem cal technic that the inclusion bodies, wh ch probably represent masses f accumulated iruses, contain desoxyribonucleic acid, as is generally believed. It ppears that the masses of

(6) Acta dermat venereol 37 231 41, 1957

viruses metabolize the thymonucleic acid of the nucleus and even the ribonucleic acid but they transform them into a compound that is histochemically different from desoxyribonucleic acid

How Communicable Are Warts? Roy E. Kile[7] (Univ of Cincinnati) asks this question as he observes the folklore of warts and comments on the literature indicating their viral basis

Among 58 children in an orphanage 15 (25.8%) showed warts distributed on various parts of the body a few were on the plantar areas and 1 on the lip In many the history of prior occurrence is not clearcut Similarly in a seminary 4 of 18 occupants of one cottage had warts occurring in 3 after entrance

Autotransmission of warts is common combing the hair shaving and similar acts definitely transplant the virus. The spread of lesions from one person to another is difficult to establish although it does occur On the basis of present information it is not possible to say whether or how precautions to avoid spread should be taken particularly in an institution However simple hygienic precautions should be observed by persons with warts There may be many strains of wart virus of variable communicability which may account for the complexity of the problem

► [The 25.8% incidence of warts among young people 6-15 years of age seems unusually high. Among the possible explanations for this high incidence are (1) an unusually virulent virus, (2) an unusually careful examination of each subject carried out by a competent and interested dermatologist, (3) the living and hygienic conditions in the orphanage and (4) the nature of the orphans personal and institutional duties and responsibilities perhaps necessitating frequent and close contact among the children.—Eds.]

Cytologic and Cytochemical Investigation of Development of Viral Papilloma of Human Skin Some types of verrucae of human skin have long been known to be caused by a filterable infectious agent and as such represent the only kind of tumorous growth in man definitely known to be virus induced. Warts of this kind characterized cytologically by intranuclear inclusion bodies and cytoplasmic masses have been shown to yield crystalline viral particles

David P Bloch and Gabriel C Godman[8] (Columbia Univ) describe the morphologic appearances and some tinctorial properties of the cells of the infectious (viral) papilloma of

(7) J.A.M.A. 162 1222-1224 Nov 24 1 56
(8) J Exper Med 105 161 176, February 1957

human skin Pathologic alterations of the nuclei of affected cells occur in a definite sequence of stages. These can be followed progressively from the lower layers of the stratum spinosum into the stratum corneum. In the earliest stage an acidophilic Feulgen-negative intranuclear inclusion body is recognizable. Subsequently the inclusion body and nucleus enlarge, there is progressive disorganization of nuclear structure, and the inclusion body then becomes basophilic and stains with the Feulgen reaction The nucleus finally disappears, leaving the inclusion body in the cell remnant.

The relative amounts of Feulgen-colored desoxyribonucleic acid (DNA) per cell at each stage in the evolution of the lesion in the infected cells, as well as in normal-appearing and hypertrophic cells of the papilloma were measured microphotometrically in Feulgen preparations. Determinations were made using the plug and "two wavelength" methods. These were compared with measurements of DNA in cells of the basal and spinous layers of normal human skin

The frequency distribution curves of relative amount of DNA in cells of normal skin, and normal-appearing cells in hyperplastic epithelium, show the bimodal diploid and tetraploid peaks characteristic of growing tissues.

Infection of the epidermal cell entails prompt synthesis of DNA in the nucleus Increased amounts of DNA (tetraploid to 16-ploid levels) are found in the earliest recognizable cytopathologic stages of infection and do not increase appreciably during subsequent evolution of the cellular lesion At a relatively late stage, all the cellular DNA is relocated in the inclusion body and is not further significantly increased in amount Neoformation of DNA would appear to require a nucleus relatively little altered and does not proceed when more profound structural changes become evident.

The stimulus to the hyperplastic proliferation of the cells that constitute the papillomatous tumor is unknown. It may result from liberation of growth promoting substances from cells damaged by virus, or conceivably it might result from masked or inapparent viral infection of some cells or may be a prior stage of infection in which only a stimulating action rather than the usual destructive effect is manifested.

* [Molluscum contagiosum and milkers nodules also are tumors which occur on skin and are virus-induced —Eds.]

Epidermodysplasia Verruciformis Lewandowsky Lutz S Jablonska and B Milewski[9] (Univ of Warsaw) report 4 cases, 2 of which are remarkable not only because of their clear origin but also because of positive results of auto- and heteroinoculation These 4 cases showed all the characteristics on which the diagnosis of epidermodysplasia verruciformis is based clinical manifestations of the type of gen-



Fig 56. (Courtesy of Jablonska, S and Milewski, B. Dermatologica 115 1 22, July 1957)

eralized flat warts histologically marked vacuolation of epidermis cells particularly in the granulosum and prickle cell layers onset of the disease in childhood or around puberty frequently observed familial character of the condition with occurrence in brothers and sisters continuous existence of lesions which present hardly any essential changes marked resistance to therapy Minor morphologic differences may occur e g lesions on the legs in Case 2 were larger more prominent and more hyperkeratotic (Fig 56) These and other differences may be due to general constitutional conditions and to variation of the areas in which the lesions develop Re-

(9) Dermatologica 115 1 22, July 1957

sistance to treatment may similarly be explained. Consanguinity or formation of malignant tumors was reported in only a very small percentage of cases

When epidermodysplasia verruciformis was described in 1922 by Lewandowsky and Lutz, the condition was thought to be a congenital epidermal anomaly a genodermatosis. Twenty four years later Lutz reported successful autoinoculation in a case of familial disease and assumed the condition to be a type of generalized warts. In Cases 1 and 2 various essential facts strongly support this assumption (1) The lesions appeared after a mashed wart had been rubbed onto the back of the hands and feet of both patients. (2) Identical verrucous lesions appeared in the patients—a young girl (Case 1) and her older sister (Case 2)—on whose hand and feet the mashed wart had been rubbed at the same time (3) Infection thus occurred from a verruca vulgaris that had been removed from the finger of their brother (virus of verruca vulgaris, verruca plana and condyloma acuminatum is recognized to be the same morphologic differences are due to differences in the area in which the virus establishes itself) (4) Disseminated lesions in Cases 1 and 2 clinically corresponded to generalized flat warts which are comparatively easy to scrape off (5) Histologic changes corresponded fully to those seen in flat warts and in epidermodysplasia verruciformis. (6) Results of hetero- and autoinoculation experiments were positive.

For autoinoculation, material of an excised and finely crushed warty lesion was rubbed into the scarified skin of the thigh and kept moist for 48 hours by covering with wet gauze and watch glass Two areas were scarified (one more superficially the other more deeply) and inoculated and a third, scarified but not inoculated, served as control. For heteroinoculation the same procedure was carried out on the upper arms and forearms of 3 healthy persons. About 10 days after inoculation small, shiny papules appeared along scarification lines (Fig 57 *A*) in 2 of the test persons and enlarged slowly (*B* and *C*) Biopsies (taken on the 14th and 21st day after appearance) revealed acanthosis hyperkeratosis and some vacuolation of *rete cells* marked inflammatory changes with round cell infiltrates in the stratum papillare. Autoinoculation was also positive producing papular lesions in scarified areas after about 2 weeks which were very similar to the

original spontaneous lesions and corresponded histologically to changes in heteroinoculation.

Auto- and heteroinoculation experiments carried out with material from one of the more prominent lesions of the leg on the patient in Case 2 and the same 3 test persons were positive only in 1 of the latter papules which appeared about 20 days after inoculation corresponded histologically to those seen in inoculation experiments on Case 1 with slight vacuolation of rete cells.

Because of good effects of grenz ray therapy in Case 1 the authors suggest erythema doses of 600-1 000 r which should be repeated according to intensity of reaction at intervals of

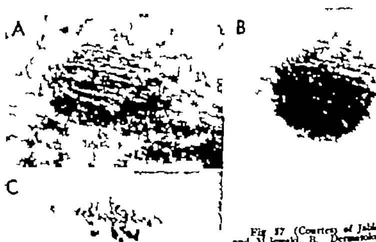


Fig 57 (Courtesy of Jablonska, S and Milewski, B Dermatologica 115 1 22, July 1957)

at least 3 weeks For extensive irradiation areas smaller single doses (600-650 r) are recommended In Cases 3 and 4 grenz ray treatment was not successful probably because doses (200-300 r) were too small (suberythematous)

►[These studies, together with those of Lutz in 1946, show convincingly that some and perhaps all epidermodysplasia verruciformis actually widespread infection with wart virus on highly susceptible persons Clinical experience in cases of verruca vulgaris and plantaris also demonstrates that some persons have an unusual susceptibility to infection with wart virus while others appear to be relatively or absolutely immune

If epidermodysplasia verruciformis is produced by the same virus as that causing verruca vulgaris and verruca plana and if on occasion one of these lesions of epidermodysplasia becomes malignant, then one must con-

under the possibility that on rare *pible terrain* verruca vulgaris lesions could give rise to lesions which eventually may turn malignant.—Eds.]

Pyoderma Chancriformis Faciei. W Frain Bell[1] (St. John Hosp., London) describes 3 cases. The disease usually occurs in adults. Most lesions are solitary and appear on the face although they may appear elsewhere. The common est site is the eyelid (Fig 58) The initial lesion is a papulo-pustule or vesicle which ulcerates after a quiescent period of a week or two Ulceration is usually superficial but may be deeper if the lips or genitalia are involved. The base i covered with a dark crust and a variable amount of exudate



Fig 58.—Lesion of pyoderma chancriforme faciei on eyelid (Courtesy of Frain-Bell, W Brit J Dermat. 69 19 24 January 1957)

more commonly serous than purulent. The edge of the ulcer is smooth and raised with minimal surroundi g edema and erythema, which may be more marked when the eyelid is af fected. The lesion is freely movable o er the subcutaneous tissue and feels l'ke a button imbedded n the skin. Painless enlargement of regional lymph glands is common but may be absent. The lesion tself is painless.

Following ulceration there is little change for a week or two then healing occurs rapidly with slight scarring, the total duration varying from 4 to 8 weeks. Staphylococcus ureus can be isolated in most cases.

Pyoderma chancriformis faciei appears to be a clinical entity It may simulate syphilitic chancre although confirma

( ) Brit. J. Dermat. 69 19-24, January 1957

tory evidence of syphilis is absent The clinical course and histologic findings rule out epithelioma

► [We agree with the author that the word "faciei" in the name of this disease is misleading, as these lesions do not occur exclusively on the face. Chancriform pyoderma is an entity worth keeping in mind because of the differential diagnosis with lesions which it resembles clinically such as syphilis, tuberculosis and epithelioma —Eds.]

Pyoderma Gangrenosum Clinical Study of 19 Cases (12 women and 7 men aged 16-67) is reported by Harold O Perry and Louis A Brunsting[2] (Mayo Clinic and Found.) In 11 patients (60%) clinical and laboratory evidence of chronic ulcerative colitis was present 4 had other intestinal disease and 2 gave a history of gastrointestinal disturbance

Microscopic examination of specimens taken from the active margin of lesions in 11 patients and intensive investigation for bacteria and fungi failed to clarify the bacteriologic or histopathologic aspects of the entity In 2, the lesions became aggravated and generalized after ingestion of potassium iodide Blistering eruptions indistinguishable from dermatitis herpetiformis clinically were seen in 3 patients. Two others gave histories suggestive of such an eruption. Except for arthritis and anemia, other complications were infrequent The arthritis varied in severity from persistent pain in some joints to multiple joint involvement with redness swelling pain and roentgenologic changes Arthritis preceded the skin lesions in 6 patients occurred at the same time as the lesions in 2 and followed them in 1

No treatment for pyoderma gangrenosum is effective unless the underlying disease process is also controlled. In patients with chronic ulcerative colitis and in others salicylazosulfapyridine (Azulfidine) in long courses was the most effective treatment The usual dose was 0 5 Gm every 3 hours 7-8 times daily For maintenance therapy the drug was taken for 10 days alternating with a 10-day rest period. Of 11 patients who received a satisfactory course of treatment 9 showed a good response Three patients have had recurrences controlled by salicylazosulfapyridine One case is described.

Man, 53 had had painful ulcerations of the legs for 4 years (Fig 59) and vesiculobullous lesion of the trunk for 2½ years. Diagnosis was pyoderma gangrenosum with atypical dermatitis herpetiformis. Extensive investigation failed to reveal chronic ulcerative colitis, but duodenal ulcer was discovered.

(2) A.M.A. Arch. Dermat. 75 380-386, March, 1957

Oxytetracycline was given initially because of infection in the leg lesions. With improvement, salicylazosulfapyridine was substituted. After 19 days, the leg lesions were 75% healed and the trunk lesions 50% healed. The patient was then discharged and placed on maintenance therapy 4 Gm. salicylazosulfapyridine daily for 10 days followed by 10-day rest periods. He returned 16 months later and re-



Fig. 50.—Pyoderma gangrenosum of right pretibial region, on patient's admission. (Courtesy of Perry, H. O., and Brunsting, L. A.: A.M.A. Arch. Dermat. 75:380-386, March, 1957.)

ported that he had taken 4 Gm. of the drug daily to prevent recurrences. Sulfapyridine was substituted but was not tolerated.

[This series involves cases dating back to 1930. In recent years it has been found that hypo- or agammaglobulinemia is sometimes present in pyoderma gangrenosum and that the administration of cortisone and gamma globulin is helpful in some patients.—Eds.]

Pyoderma Gangrenosum: Histology of Primary Lesion is described by G. H. Percival[1] (Edinburgh Univ.)

Man, 24, had had recurrent attacks of ulcerative colitis for 4 years. Three weeks after onset of an attack, a sparse eruption of purulent bullae appeared on the lower trunk and thighs. Some of the lesions rapidly developed into ulcers. Cultures from unruptured purulent bullae were sterile. Treatment with cortisone and later with ACTH resulted in control of the intestinal symptoms and healing of the ulcers.

Histologic examination of a purulent bulla similar to those which subsequently developed into ulcers, showed the roof of the cavity to be formed of stratum corneum and most of the floor to be composed of epidermis of varied thickness. In the middle of the floor the epidermis was absent. The epidermal cells adjacent to the central break in the floor were degener-

[1] Brit. J. Dermat. 69:130-134, April, 1957.

ate. The cavity contained many lymphocytes, leukocytes and epidermal cells. The epidermal cells occurred in clumps or as isolated cells and all showed varied stages of degeneration. There was a scanty perivascular infiltrate in the papillary layer of the dermis beneath the break in the epidermal floor.

The degenerated cells in the cavity of the bulla, the degeneration of the epidermis adjacent to the center of the floor and the entire absence of epidermis at the central break suggest that a massive degenerative process occurred, extending from the basal layer to the stratum corneum. Lateral fissuring of the adjacent epidermis below the stratum corneum could follow this process with the production of a bulla.

The findings suggest that the primary skin lesion in this case of pyoderma gangrenosum resulted from the action of some factor with a specific effect on the epidermis. Abnormal epithelial cells have been reported in the intestinal mucosa in various active phases of ulcerative colitis and have been considered primary changes rather than the result of associated inflammation.

These observations on the state of the intestinal mucosa and the primary skin lesion in ulcerative colitis indicate that primary epithelial damage may be common to both. The sterility of the lesions and the histologic appearance of the epidermal cells suggest that the epithelial disintegration results from the action of a chemical substance or virus. Lack of response to antibacterial remedies by either affected tissue supports this view. Where the skin is concerned bacterial invasion appears to be a later development. It might therefore be inferred that in both organs the lesions are produced by the same factor acting selectively on similar tissue components. If so, the fact that skin ulceration occasionally precedes intestinal symptoms lends support to the hypothesis that the cause has its origin in some other focus and attacks the intestinal mucosa and skin independently.

► [Stoughton (J. Invest. Dermat. 20:353, 1953) demonstrated that a proteolytic enzyme extracted from the feces of patients with ulcerative colitis is capable of producing acantholysis and vesicle formation in formalin fixed skin sections. The role of such an enzyme in the pathogenesis of skin lesions associated with ulcerative colitis has not as yet been elucidated. —Eds.]

Erythema Axillarum Perstans of Micrococcic Origin was seen by Aldo Castellani[4] (Lisbon) as a persistent patchy erythema in 4 patients. The patches were asymptomatic

(4) Dermatologica 113:202-206, October, 1956.

½-1 cm. or more in diameter, round or irregular, not raised, desquamating or infiltrated. The margins were sometimes well defined and several areas fused. At times there were small discrete papules or papulopustules which ultimately dried.

The disease is chronic and recurrent but may disappear in winter. Biopsy showed no specific histopathology. The diagnosis is based on the clinical picture and presence of Micrococcus violagabriellae, which is closely related to Staphylococcus aureus (M. pyogenes var. aureus) and Staph. albus (M. pyogenes var. albus). Its chief characteristic is the purplish color it produces in potato and glucose agar cultures. The organism resembles the ordinary staphylococcus microscopically. It is gram-positive, nonacid-resistant and nonmotile.

Treatment is difficult. Response to antibiotics and topical antiseptics is poor. Most effective is Castellani's paint applied twice daily (formula: alcoholic saturated solution of basic fuchsin, 10 cc.; 5% aqueous carbolic acid solution, 100 cc.; after 2 hours add 5 cc. acetone and 2 hours later 10 Gm. resorcin). Despite its duration, the disease does not affect the general health of the patient nor does it produce subjective discomfort.

► [Although we have had no occasion to treat this condition, it has been our general experience that for eruptions which can be treated successfully with staining and discoloring dye, there are other less messy topical medicaments which do an equally effective job.—Eds.]

Role of Pseudomonas Aeruginosa in Infections About Nails. Marjorie Frantz Bauer and Harold Cohen (Univ. of Southern California) report 4 cases in which infection about the nails was apparently due primarily to Pseudomonas aeruginosa. Three patients had paronychia with blue-black and green discoloration of the nail; the 4th had an acrodermatitis continua-like eruption. Cultures were positive for Pseudomonas aeruginosa in 3, whereas in the 4th no material for culture could be expressed from the nail fold. Good therapeutic results were obtained *only* when agents to which pseudomonas is sensitive were used. The most effective agents appeared to be cool soaks of 0.1% polymyxin B sulfate in 1% acetic acid, followed by 2% methylrosaniline.

The organism apparently invades the tissue about the nail after minor trauma. All 4 patients gave such a history. One

(1) A.M.A. Arch. Dermat. 75:394-396, March, 1957.

had forcibly removed a portion of the cuticle about the nail. The others had a habit of forcing the cuticle back from the nail plate and trimming it with nail scissors

Other types of organisms can produce the morphology seen in these cases but pseudomonas should be recognized as one of them since pseudomonas responds to an entirely different series of antibiotics than do the usual staphylococcic infections of the skin

► [The habit of pushing back the cuticle and clipping it with nail scissors is common in this country Traumatizing these tissues probably accounts for creation of portals of entry for infectious micro-organisms around the nail plate and for the many infections of this type seen nowadays, even in women who rarely or never do wet housework.—Eds.]

Seal Finger Report of Occupational Disease Rare in United States, but not uncommon in the Scandinavian countries is presented by John S Skinner[6] (Washington Univ) The infection occurs exclusively in men who slaughter or skin seals. A history of preceding injury can usually be obtained. After an incubation period of 3-21 days the involved finger becomes markedly swollen and exquisitely painful and tender The skin appears tightly drawn and only slightly reddened Adjacent joints are generally involved and motion is limited by pain and swelling Systemic symptoms are slight or absent. Roentgenograms usually show some joint-space narrowing and radiolucency of the bone near the joint Chlortetracycline is ordinarily effective in controlling the disease

The author s patient a youth 19 worked as a blubberer for 6 weeks before his infection appeared. During this time he sustained numerous lacerations on his fingers Although seal finger is commonly spread from older seal this patient was exposed only to the skins of young seals

Different Types of Swimming Pool Infections Caused by Mycobacteria. Two clinically distinct types of swimming pool infections have been described In cases reported by Hellerstrom and others the characteristic site of involvement was the bridge of the nose and clinically appreciable and histologically verified lupus nodules were present In at least one of these the causative organism was the human type fully virulent tubercle bacillus The cases studied by Herlitz Linell and Norden in which Mycobacterium balnei was the causative agent were characterized by lesions on

(6) A.M.A. Arch. Derm. 75 559-561, April, 1957

the elbows and knees and by the absence of lupus nodules

S. Hellerström, H. Ericsson and R. Lagercrantz (Karolinska Hosp., Stockholm) report a swimming pool infection with changes considered typical of infection by M. balnei but proved to be due to human tubercle bacilli.

Boy, 12, sustained frequent abrasions in a public swimming pool which he visited every other week. He first noticed a skin eruption on his right elbow and 1 week later on one knee. The lesions were composed of bluish red nodules (Fig. 60) not perforated by a probe



Fig. 60.—Eruption on right elbow showing apple-jelly nodules. (Courtesy of Hellerström, S., et al.: Acta dermat.-venereol. 36:249-256, 1956.)

applied with moderate pressure and not showing apple-jelly nodules on diascopic examination. Biopsy revealed foci of epithelioid cells and Langhans giant cells, but no necrosis. Special stains failed to reveal acid-fast rods. Demonstration of the causative agent proved difficult. The isolated strain initially had a markedly decreased virulence and showed abnormal cultural behavior. After further passages through animal and artificial mediums, the strain acquired properties identical with those of typical human tubercle bacilli.

The authors conclude, on the basis of the present case, that skin infections following swimming-pool injuries may present clinical pictures varying between typical lupus vulgaris and the lesions described in the literature as typical of infection with M. balnei. Neither the clinical picture nor the histologic changes permit definite inferences as to etiology in a given case. The causative agents range from typical human tubercle bacilli with variable virulence to typical M. balnei.

(1) Acta dermat.-venereol. 36:240-256, 1956.

Leprosy and Tuberculosis Antagonistic Diseases. The hypothesis that these diseases are antagonistic is discussed by Jose Maria M. Fernandez[5] (Rosario Argentina). Though conclusive proof has not yet been attained, immunologic, clinical and epidemiologic facts suggest that a previous tuberculous infection in a person attacked by Mycobacterium leprae affords some protection or resistance against the virulence of this bacillus sometimes even preventing lepra or the onset of the malignant form.

Immunologic arguments are based on the fact that spontaneous tuberculous infection or one induced by BCG exercises a positivizing influence on the lepromin reaction. If the capacity of resistance by the organism to M leprae is shown by a positive lepromin reaction, this influence on the reaction means that the tuberculous factor obstructs or inhibits the pathologic action of M. leprae.

Clinical arguments are based on comparative study of the development of leprosy in tuberculin positive and tuberculin negative persons living with lepers. The index of infection and its gravity are greater in tuberculin negative persons. If persons living with lepers are vaccinated with BCG, they are more protected than those not vaccinated since lepromatous forms have been found among the latter but not among the former In another study the only lepromatous cases found in children living with lepers were in those who were tuberculin negative

Comparative epidemiologic study of leprosy and tuberculosis in different countries also supports the hypothesis of antagonism between the diseases. Tuberculosis is much more infectious and virulent than leprosy Therefore when both attack a population tuberculosis develops more rapidly and intensely As a large section of the population acquires an infection of tuberculosis it derives a degree of resistance to leprosy The result is a gradual elimination of leprosy as tuberculosis becomes more generalized England and Germany were the first European nations to reach the top of the curve of tuberculosis incidence and the first in which leprosy disappeared In East and Central Africa tuberculosis is rare the tribes who have not had contact with Europeans are almost completely free from it Both these places have the highest index in the world for leprosy

(5) A.M.A. Arch. Dermat 75 101 106, January 1957

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(8) A.M.A. Arch. Dermat. 75 101 104, January 1957

Electrophoresis and more recently developed paper microelectrophoresis permit the recognition of protein changes in leprosy which generally consist of diminution of albumin normal values of alpha and beta globulin and marked increase of gamma globulin. In cases of leprosy associated with pulmonary tuberculosis the proteinoglucidograms showed a increase of $alpha_1$ globulin in those in which hepatosplenorenal amyloidosis developed, proteinolipidograms revealed a considerable ncrease of $alpha_2$ globulin and augmented β-lipids.

Repeated biologic tests are recommended, not only to control the disease course, but also to assess therapeutic effectiveness particularly in cases in which results appear clinically excellent and nasal and cutaneous smears are negative

Cutaneous Brucellosis. An interesting case is reported by I L. Burger[3] (Univ of Tubingen)

Woman, 45 had history of pneumonia and pleurisy at age 2½ and frequent sore throat later For 2 year before hospitalization she complained of tiredness, anorexia, constipation, chills, occasional nosebleeds, headaches and pai in the right elbow In August 1955 about 6 weeks before the first admission, she had nummular dark bluish red erythema on the extensor surface of the right upper arm with slight epidermal atrophy telangiectasia and rather well-defined, firm, platelike infiltration. Histologically the infiltration had a multicentric structure, the individual infiltrates originating mainly from follicles and consisting of histiocytes and numerous plasma cells or plasma cell-like elements The subepidermal linear zone was free from infiltration There was complete healing after 3 fractional superficial -ray doses of 100 each. When hospitalized again in May 1956, the patient had anorexia, considerable weight loss, constipation, multiple lymphadenopathy enlarged palpable spleen, and an ill-defined, firm, painful swelling on the left lateral margin of the manubrium sterni Body temperatures were between 96 8 and 100 4 F and the blood sedimentation rate was 35/55 mm Leukopenia and hypochromic anemia existed On the last hospitalization in August 1956, temperatures were normal and the lymphadenopathies had disappeared. On the sternum a bluish red protuberance with central softening had appeared Biopsy of the abscess showed it to be bacteriologically negative at first, but later cultures revealed melitensis strains. Histologic examination showed central necrotic, partly liquefied zone with numerous vessels, epithelioid nodules, bizarre or Langhans giant cells and peripheral zone with predominance of histiocytes. Coccoid bacilli stained ed by the Hansen method (brucellae) were found in areas rich in plasma cells, particularly in the peripheral zones of the abscess. Serum agglutination was positive (1:80) and epicutaneous tests with "febris undulans diagnosticum Hoechst" were strongly pos-

3) Arch klin exper Dermat 204 13 1 1957

case, no restrictions are placed on leprosy patients, except that they are not allowed to engage in occupations involving food handling.—Ed.]

Biologic Controls in Treatment of Leprosy The chaulmoogra therapy of leprosy has been superseded by more modern drugs e.g thiosemicarbazone streptomycin and isonicotinic acid hydrazide which despite clinical effects (healing of cutaneous manifestations reversal of positive nasal and cutaneous smears to negative) cannot prevent recurrences or eliminate persistent deep visceral bacillary deposits.

Ed Benhamou B Ferrand A Sorrel and J-Cl Chiche[1] (Algiers) report 8 cases which demonstrate the necessity of checking therapeutic effects in leprosy by repeated biologic controls

Nasal smears represent a simple approach but they are often unreliable in cases of tuberculoid or undifferentiated leprosy Cutaneous smears may be taken after scarification of peripheral parts of lesions after reaspiration of 0 5 cc. saline injected subcutaneously into the lesion or by crushing small particles of the lesion on a slide

Cutaneous biopsy permits diagnosis as well as control of pathologic changes Lepromas reveal Virchow cells and numerous bacilli often in "globi In tuberculoid leprosy in which the Mitsuda reaction is often positive bacilli are scarce or missing the latter is also true of undifferentiated types.

Bone marrow puncture often discloses the presence of bacilli in large reticulohistiocytic elements but is mostly negative in tuberculoid leprosy The puncture of enlarged lymph nodes in leprosy often shows polyadenopathy It reveals no characteristic cytology but demonstrates abundant bacilli very early in lepromatous and occasionally tuberculoid types and even in clinically normal contact persons. Spleen puncture is positive in severe cases in which lepromas of the spleen were seen at autopsy but also often in less severe cases and in patients who showed definite posttherapeutic improvement As in other parts of the reticuloendothelial tissue bacilli are found extracellular or more frequently intracellular in Virchow cells

Liver puncture biopsies were positive at the beginning of antilepromatous treatment and remained positive for 8-10 months. At autopsies Hansen bacilli were found in Virchow cells of inflammatory lymphocytic histiocytic nodules and also in enlarged Kupffer cells in liver sinusoids

(1) Presse med 64 1728-1732, Oct 24 1956

persists, with variations, until the acute phase of the disease subsides.

The cutaneous eruption the most characteristic finding and prerequisite to early diagnos s usually appears on the 2d-4th day It develops first on the flexural surfaces of the wrists and ankles and spreads within 2 3 day s to other areas. The palms and soles a e usually involved. The initial lesions are discrete erythematous macules a few millimeters in diameter that blanch on diascopy Within hours to a few days at most, the lesions assume a purpuric hue and no longer blanch on pressure. If the disease is severe and progressive the lesions may become maculopapular increase in size and coalesce ultimately involving the entire skin surface. Gangrene of th terminal parts of the body may occur The oral and pharyngeal mucosa may be involved, especially in se ere cases

Edema, prostration lethargy delirium photophobia hyperesthesia of the skin and muscles, enlargement of the spleen and neurologic changes may be seen in the disease course. The verage mortality rate in untreated pat ents is about 13% for those under 40 and 41% for those over 40

Persistent fever and a characteristic skin eruption are the most reliable ea ly clinical manifestations. No laboratory procedu e is consistently reliable in making the diagnosis during the first week or 10 days of illness. A h gh index of suspicion on the part of the phys cian, a history of recent exposure to ticks and an accurate evaluation of clinical manifestations are of paramount importance in early diagnosis. Among diagnostic tests the proteus agglutination reaction is the most widely used and results a e usually positive by th 10-15th day of the disease. Treatment should be undertaken promptly without awaiting final diagnosis The advent f antibiotics, particularly chlortetracycline hydrochloride oxytetracycline and chloramphenicol, has greatly improved the prognosis

Among 74 of th authors cases there were 7 deaths 5 occurred in patients past age 55 1 in a patient aged 44 and 1 in a child of 6.

► [When removing ticks from the skin it is important that the mouth parts of the tick are not left behind in order to avoid local foreign body type reactions. The tick usually can be removed in toto if its body is heated gently with, e. the lit end of cigaret held close. This prompts the tick to "let go —Eds]

itive after 48 hours showing densely disseminated pinhead- to rice grain-sized erythematous nodules. Investigation revealed the existence of an undulant fever epidemic in the district where the patient had formerly lived.

Brucellosis includes Bang's disease (Brucella abortus Bang) Malta undulant fever (Br melitensis Bruce) and hog brucellosis (Br suis Traum) In a marked parallelism to cutaneous tuberculosis the skin manifestations of brucellosis may according to the various stages be divided into (1) brucellar eruptions in veterinarians, milkers etc. which correspond to primary lesions (2) exanthema like generalized eruptions petechiae roseolae and scarlantiniform or morbilliform types representing the secondary stage of the disease and (3) isolated cutaneous lesions (like the scrofuloderma like abscess in the case described) which may be considered tertiary in character and which correspond to manifestations of the disease in other organs, e g Bang's orchitis and abscess forming ovarian cysts

Transitory erythematous lesions appearing shortly after contact with infected animals and disappearing within a few hours are probably nonspecific. Eczematoid and pemphigoid reactions are characterized by their chronic, therapy resistant course.

► [Brucellosis is an infectious disease often accompanied by cutaneous manifestations. The true nature of these cutaneous lesions may well be overlooked unless the dermatologist has a high index of suspicion or practices in an area where brucellosis is endemic.—Eds.]

Rocky Mountain Spotted Fever According to Edward P Cawley and Clayton E Wheeler[3] (Univ of Virginia) 4,517 cases of this fever were reported in the United States during 1945-54 About half occurred in the South Atlantic States. Most cases are encountered during the warm months when dog ticks (Dermacentor variabilis) and wood ticks (Dermacentor andersoni) are prevalent The causative organism is Rickettsia rickettsii The incidence of the disease is higher in children in the South Atlantic States than in the Rocky Mountain States. This is explained on the basis of the proximity of the vectors to humans of various age groups.

The clinical picture of Rocky Mountain spotted fever varies from a mild to a severe and sometimes fatal illness. The usual incubation period is 4-8 days Onset is usually brusque with headache, chills and aches and pains in muscles and joints The fever reaches 103-104 F in the first 24 hours and

(3) J.A.M.A. 163 1003-1007 Mar 23 1957

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Disseminated Anergic American Leishmaniasis Report of Three Cases of Type Clinically Resembling Lepromatous Leprosy is presented by Jacinto Convit, Oscar Reyes and Francisco Kerdel[2] (Caracas Venezuela) The characteristic lesions were erythematous macules diffuse infiltration plaques, papules and nodules with a keloidal xanthomatous or verrucous appearance Occasionally lesions broke down when exposed to trauma. The lesions varied from straw yellow light red, port win to violaceous in color The sites of predilection were the face ears, elbows and knees but generalized lesion were also observed. The mucosa of the nose was cli cally unaffected although leishmania was found in smears No lesions were seen on the scalp axillae palms and soles The clinical resemblance to lepromatous leprosy was so marked that 1 patient was mistakenly interned in a leprosarium before the true nature of the disease was determined.

The disease course was extremely chronic and progressive with occasional periods of exacerbation The general health was not affected. A negative response to the intradermal test with leishmanin was shown consistently by all 3 pat ents. Smears and histologic examination in all stages of the disease showed many parasites. In cases previously reported and in the present cases, a striking failure of all therapeutic measures was noted.

The authors consider this an anergic form of lei hmaniasis, which possibly explains the extensive distribution, abundance of parasites n the lesions, extreme chronicity and resistance to therapy

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Cat Scabies in Man is reported by J F H Sanderink and F H Oswald[3] (Uni of Groningen) in a family of adults nd 3 hildren who complained f itch lasting over 2 weeks The skin hanges and history immediately suggested scabies but non of the patients displayed a typical picture of scabies due to mites and the usual sites (wrist and genitalia) were not affected Eruption was most pronounced in a boy 11 who exhibited di seminated, lenticular rather thickly clustered, somewhat edematous prurigo-like papules, especially on the chest, back and upper arms. The other patients

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[2] A M A Arch Dermat 76 213 21 August, 57
[3] Nederl tijdschr geneesk [illegible] Dec 29 1956.

Osseous Lesions of Leishmaniasis. Newton A. Guimarães and Yves P Silva[4] (Univ of Bahia) state there are few reported cases of osseous lesions in leishmaniasis even in Brazil where the cutaneous form of the disease has always been common. In all but 1 of the reported cases, the osseous lesions seem to have originated in contiguity with skin lesions. However most of the osseous lesions in a child observed by the authors were not contiguous to any skin lesions.

In girl 6, a "wound appeared on the left arm 4 months after a fall. Despite local treatment and large quantities of penicillin and a sulfonamide, it continued to increase in size. Before admission, the patient's brother had previously been admitted with cutaneous leishmaniasis. Examination showed the patient to have both osseous and cutaneous lesions characteristic of leishmaniasis. The multiplicity of the osseous lesions, affecting not only the digital bones but also the cubital diaphysis as shown by radiographs, was a striking feature of the case indicating that the lesions were hematogenous in origin.

The leishmaniatic nature of the osseous lesions was established on the following basis (1) they appeared in a patient who had typical manifestations of leishmaniasis in the skin and nasal mucosa who presented a positive Montenegro reaction and who came from a recognized center of the disease since a brother living in the same house was also affected (2) although a search for the parasites in one of the skin lesions was negative this circumstance was not particularly significant as it is often seen in cases in which the lesions are of fairly long standing especially if treated topically and (3) not only were other possible causes excluded, but the osseous lesions regressed concurrently with those in the skin and nasal mucosa with only the use of a substance active against the protozoiasis (N methylglucamine antimonate or Glucantime) Also the radiologic picture of the lesions resembled that described by other workers especially Rafael de Barros who said that although the osseous lesions of leishmaniasis are not strictly specific they can be distinguished from other common bone lesions, i e., from syphilis in which the osteitis is much more intense and which presents frequent and also intense ossifying periostitis from tuberculosis, since the focal caries and lesions of rarefaction found in tuberculosis are lacking in osseous leishmaniasis and from osteomyelitis in which destructive cavities and sequestra are present"

(4) A brasil dermat [illegible] 32 1 7 March, 1957

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(13) A.M.A. Arch. Dermat. 313-317, August, 1957
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Osseous Lesions of Leishmaniasis. Newton A. Guimarães and Yves P. Silva[4] (Univ. of Bahia) state there are few reported cases of osseous lesions in leishmaniasis even in Brazil where the cutaneous form of the disease has always been common. In all but 1 of the reported cases the osseous lesions seem to have originated in contiguity with skin lesions. However, most of the osseous lesions in a child observed by the authors were not contiguous to any skin lesions.

In girl 6 a "wound" appeared on the left arm 4 months after a fall. Despite local treatment and large quantities of penicillin and a sulfonamide, it continued to increase in size. Before admission, the patient's brother had previously been admitted with cutaneous leishmaniasis. Examination showed the patient to have both osseous and cutaneous lesions characteristic of leishmaniasis. The multiplicity of the osseous lesions, affecting not only the digital bones but also the *cubital diaphysis* as shown by radiographs, was a striking feature of the case, indicating that the lesions were hematogenous in origin.

The leishmaniatic nature of the osseous lesions was established on the following basis: (1) they appeared in a patient who had typical manifestations of leishmaniasis in the skin and nasal mucosa, who presented a positive Montenegro reaction and who came from a recognized center of the disease, since a brother living in the same house was also affected; (2) although a search for the parasites in one of the skin lesions was negative, this circumstance was not particularly significant as it is often seen in cases in which the lesions are of fairly long standing, especially if treated topically; and (3) not only were other possible causes excluded, but the osseous lesions regressed concurrently with those in the skin and nasal mucosa with only the use of a substance active against the protozoiasis (N-methylglucamine antimonate or Glucantime). Also the radiologic picture of the lesions resembled that described by other workers, especially Rafael de Barros, who said that although the osseous lesions of leishmaniasis are not strictly specific, they can be distinguished from other common bone lesions, i.e., from syphilis, in which the osteitis is much more intense and which presents frequent and also intense ossifying periostitis; from tuberculosis, since the focal caries and lesions of rarefaction found in tuberculosis are lacking in osseous leishmaniasis; and from osteomyelitis, in which destructive cavities and sequestra are present."

(4) A. brasil. dermat. sif. 32:1-7, March, 1957

Veterans Administration. Finally 27,786 veterans were located and examined.

All had a blood serologic test for syphilis (STS) and almost half had a cerebrospinal fluid examination. In 18.8% the STS was positive and in 2.7% doubtful. The cerebrospinal fluid examination was positive or doubtful in 4.2%. Veterans whose blood test for syphilis was positive at the time of the cerebrospinal fluid examination had the highest percentage of abnormal cerebrospinal fluids. The cerebrospinal fluid positivity rate was higher in Negroes than in whites. The longer the time lapse between initial treatment and follow up the higher the percentage with positive tests.

It was estimated that a minimum of 3% of veterans treated for syphilis had neurosyphilis, indicating that about 15,000 have cerebrospinal fluid evidence of neurosyphilis at present. Thus a large group will require the expensive care implied in the progression of this disease.

► [Interesting statistics, not only from medical and humanitarian point of view but also from socioeconomic standpoint. According to the authors it costs about $40,000 to maintain paretic patient in VA facilities. With 5,000 World War I veterans now hospitalized for insanity due to syphilis the bill for their care is $200,000,000.—Eds.]

Control of Congenital Syphilis by Treatment of Syphilitic Pregnant Women. F. M. Haagsma (Univ. of Amsterdam) reports a study of 928 syphilitic women, followed at regular intervals throughout 978 pregnancies. Sufficient data about 746 infants from 734 pregnancies in 696 women were available for analysis. Patients were classified into two main groups, according to whether they were treated with penicillin or exclusively with arsenic bismuth compound and subclassified with regard to time of treatment, i.e. only during, before and during, or only before pregnancy.

Among 167 women treated only during pregnancy with at least 4,800,000 units of penicillin, only 1 infant was born with definite congenital lues. One penicillin course was the only treatment received by 59 of these women. In the neoarsphenamine group 62 women with early lues were treated during pregnancy. Of 34 who had less than 1 or only 1 course 15 had an infant with congenital lues (4 of whom died shortly after birth), whereas all 28 who received at least 2 combined neoarsphenamine and bismuth courses bore healthy children.

(8) Nederl. tijdschr. geneesk. 100 3068-3077 Oct. 27 1954.

had a similar dermatosis but one which was less marked.

Questioning revealed that the family had a cat with a skin eruption which on examination consisted of crustaceous lesions on the head, ears and neck with these patches devoid of hair and purulent conjunctivitis. The animal was so sick it had to be destroyed. In crusts obtained from the cat, many mites were found. These were identified as a cat parasite Notoedres cati, that can also affect other animals and man.

It is impossible to diagnose skin lesions in man as animal scabies, which can usually be determined only by the history of familial infection. Skin lesions in men heal rapidly when an affected animal is removed from the environment, as occurred with these patients. Rapid cure is explained by the fact that the mites die off rapidly since they cannot maintain themselves on human skin.

Histologic examination of the cat skin revealed mites in all stages of development. Skin from one patient showed urticarial edema and slight perivascular infiltrates—leukocytes with decayed nuclei. No mites were found in the skin area examined.

► [What accounts for the inability of the cat parasite to live on the skin of man or the inability of the skin of man to supply suitable conditions for survival and procreation of the cat parasite? Unfortunately nothing is known about this interesting and important aspect of parasitic infestation. —Eds.]

8. VENEREAL DISEASES AND THEIR TREATMENT (EXCLUSIVE OF GONORRHEA)

Report of Syphilis Follow up Program among Veterans after World War II is presented by S. Ross Taggart, Stanley B. Russell and Eleanor V. Price[7] (Washington, D.C.). During 1940-46 some 500,000 members of the Armed Forces acquired or were treated for syphilis. Veterans who would benefit most from follow up were studied comprising (1) those whose cerebrospinal fluid had not been examined, (2) those with previously reported positive or doubtful cerebrospinal fluid findings and (3) those who had received "inadequate" treatment. This reduced the number studied to 122,000, of whom 81,715 were investigated by states at the request of the

(7) J. Chronic Dis. 4:379-388, December 1956.

before and part also during pregnancy with neoarsphenamine or penicillin. Only 5 were seronegative at time of confinement, but all 77 children born to this group appeared completely normal.

► [One more study attesting to the superiority of penicillin over the older forms of antisyphilitic treatment. If one considers this fact, plus the much greater safety of penicillin therapy one is puzzled as to why in some parts of the world there is still some resistance to treatment with penicillin exclusively and older methods are still being used.—Eds.]

Current Status of Therapy in Syphilis is reviewed by Evan W Thomas (New York State Dept. of Health) The therapeutic agent of choice for all types of syphilis i penicillin unless the patient is sensitive to th drug Treatment schedules advised are minimal and based on experience with relatively large series of cases followed ? years or more after therapy Follow up data is relatively meager for patients treated with benzathine penicillin but this lowly absorbed preparation promises to supersede other types of penicillin in treatment of syphilis. A single treatment with 2,400 000 units of benzathine penicillin C provides demonstrabl blood concentrations of pen cillin for at least 15 days. Because of low absorption blood level are low but sufficiently high for treatment of most cases, with the possible e ception of lapses and nfections of the cardiovascular and central nervous systems

A ingle treatment with 2,400 000 units of benzathine pen icillin G can be used for outine treatment of early ymptomatic syphilis If proca ne penicill n G in oil and alum num monostearate is used, the advised dosage is 4,800,000 units given in doses f 1,200,000 units every 2 7 days. Retreatment is ndicated when rise of titers over previous level occurs or when clinical relapse is observed Relapse should be treated more ten ely with procain penicillin G in oil and alumin m monostearate rather than with benzathine pen cill G because of the h gher concentration of penic'l lin obta ned with the former preparation.

When diagnosis i latent syphilis, asymptomatic neurosyph li hould be ruled out by erebrospinal fluid examination and cardio ascula syphil s by fluoroscopy and teleroentgenography Treatment schedul advised for secondary syphilis may be used for latent syphil s When diagnosis is doubtful a total dosage of 6,000 000 unit of procaine penicillin G i oil a d aluminum monostearate in doses of 1,200

J A M A 162 1536 339, Dec 22, 1956

If the woman comes for treatment in the last 3 months, there is scarcely time for 1 course. Chance is great that the child is already infected and that neoarsphenamine will have slight effect on the fetus Only penicillin treatment has a chance of success for it passes through the placenta and can attain good concentration in fetal tissue, so that it may be effective even when the child is already infected. Of 167 pregnant women treated with penicillin 102 were treated only during the last 3 months and 59 had only 1 course of 4,800 000 units 23 were confined a month after the last injection In the neoarsphenamine group 12 of 26 women treated during the last trimester bore an infant with lues. Of 162 who had a sound child after penicillin treatment 131 had a positive serum reaction Among 46 in the neoarsphenamine group with healthy children serology was positive in 23 Two women treated with neoarsphenamine-bismuth who showed negative serum reactions before confinement had children born with syphilis

Women treated before and during pregnancy with penicillin all had nonsyphilitic children. Of 47 women previously treated with neoarsphenamine who were seen during the last trimester and received only 1 course or less, 7 had a child with congenital lues

Results were also favorable in 60 women treated with penicillin only before pregnancy only 2 had syphilitic children and 1 of these had had only 1 course of 4,800 000 units before pregnancy occurred Of 146 women with early syphilis in the neoarsphenamine group not treated during pregnancy 18 who had had only 1 course or less had 4 syphilitic babies. Of 128 who had had at least 2 courses of neoarsphenamine bismuth 7 bore syphilitic infants In 6 of these the mother was not followed during pregnancy and reinfection was probable.

In general a woman who is completely treated before pregnancy and in whom the test has become negative after 2 courses of neoarsphenamine bismuth does not need to be treated during pregnancy provided regular check ups are maintained All 115 pregnant women in whom treatment was satisfactory had a healthy infant

In women with late lues no child was born with congenital syphilis Two babies died after birth obviously of other causes. Most of 36 women with congenital lues were treated

paratively high percentage of patients. In 170 more or less advanced active changes in the cerebrospinal fluid were found. In 46, only minimal neurologic changes such as Argyll-Robertson pupils, insignificant lesions of single cranial nerves or early symptoms of tabes dorsalis, were noted. These were accompanied by unchanged cerebrospinal fluid. This proves that active pathologic processes in this group of patients died out spontaneously at a comparatively early stage and that without a detailed neurologic examination these changes may possibly not have been noted. In 21 neurosyphilitic patients, cerebrospinal fluid examination revealed partial spontaneous remission only low titer seropositive reaction and insignificant changes in the Lange test cell count and total protein level. In 39 patients the cerebrospinal fluid was normal but advanced clinical symptoms, usually tabes dorsalis were present.

Analysis of 26 married couples showed that despite being infected by the same strain of spirochete for a similar length of time the course of the disease differed in husband and wife. In general, the disease was milder in women. These findings again stress the fundamental importance of the individual immunobiologic processes which occur during the long course of syphilitic infection.

► [The importance of the difference in host reaction to disease is demonstrated by the work-up of the 26 couples who had untreated syphilis, presumably due to the same strain of spirochetes and probably for about the same length of time. The reasons for the differences in the course of syphilis in different persons are unknown, as are the reasons for the differences in susceptibility to allergic sensitization to innocuous agents as, e.g. drugs.—Eds.]

Antibody Titer in Patients with Syphilis Treated with Cortisone. Carl Rossett and Giambattista Marson[2] (Univ. of Padua) studied the effects of 200 mg. cortisone/day orally on the antibody titer of 15 patients with treated and untreated syphilis. The quantitative evaluation of antibodies was made after the immobilizing test, complement fixation and flocculation tests before and after 5 and 10 days of treatment (after 1,000 and 2,000 mg. cortisone). Only slight or no changes in the titer of complement fixing and immobilizing antibodies were observed. Instead, the drug caused an inconstant decrease in the titer of antibodies evoked by the flocculation reaction. The authors suggest that the latter effect could be ascribed to a greater sensitivity of the floccula

( ) Minerva dermat. 391-394, October 1956.

000 units at intervals of 2 7 days should be sufficient for patients with asymptomatic involvement of the central nervous or cardiovascular systems Indications for retreatment of latent syphilis are development of symptoms attributed to syphilis or sustained increases in serologic titers over previous levels

Valid data on the effects of treating late symptomatic syphilis especially neurosyphilis and cardiovascular syphilis with benzathine penicillin G are not yet available but 3 treatments with 2 400 000 units at intervals of no more than 7 days have been recommended Good results have been obtained with total doses of 6 000 000-10 000,000 units of procaine penicillin G in oil and aluminum monostearate Individual doses of 1,200 000 units should be given 2 or 3 times a week

Congenital syphilis can be treated in the same way as acquired syphilis except smaller doses should be used in children weighing under 32 kg Infants and children should receive total doses of 75 000 to 100 000 units of penicillin/kg

Patients with syphilis who are sensitive to penicillin can be treated with oxytetracycline hydrochloride chlortetracycline hydrochloride chloramphenicol erythromycin or carbomycin Available data are confined to the first two Minimal schedules with oxytetracycline hydrochloride or chlortetracycline hydrochloride consist of 3-4 Gm /day in divided doses of 0.75-1 Gm every 6 hours for 10-12 days in early and latent syphilis and for at least 15 days in neurosyphilis and cardiovascular syphilis Preliminary reports suggest that 2 3 Gm carbomycin/day for the same periods may be effective

Occurrence of Late Syphilis in Untreated Syphilitic Patients Among 500 syphilitic patients aged 26 or over formerly untreated and unaware of the existence of the disease Józef Towpik[1] (Warsaw) found 164 (33%) with latent syphilis and 336 (67%) with late syphilis Of the latter 234 had neurosyphilis 91 had cardiovascular syphilis and 9 had late benign syphilis Cardiovascular and neurosyphilis were found in 64 patients

Spontaneous regression of pathologic changes in the cerebrospinal fluid and the dying-out of active pathologic changes in the central nervous system were noted in a com

(1) Brit. J Ven. Dis. 33 2-4 March, 1957

paratively high percentage of patients. In 120 more or less advanced active changes in the cerebrospinal fluid were found. In 46, only minimal neurologic changes such as Argyll Robertson pupils insignificant lesions of single cra nial nerves or early symptoms of tabes dorsalis, were noted. These were accompanied by unchanged cerebrospinal fluid. This proves that active pathologic processes in this group of patients died out spontaneously at a comparatively early stage and that without a detailed neurologic examination, these changes may possibly not have been noted. In 21 neurosyphilitic patients cerebrospinal fluid examination revealed partial spontaneous remission, only low titer seropositive reaction and insignificant changes in the Lange test cell count and total protein le el. In 39 patients the cerebrospinal fluid was normal, but advanced clinical symptoms, usually tabes dorsalis, were present.

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3) Minerva dermat 31 393 394, October 1956.

tion reaction or to a particular cortisone induced state of the serum or to differentiation between the antilipid antibodies that fix completement and those that produce the flocculation reaction.

Sensitivity and Specificity of Reiter Protein Complement Fixation (RPCF) Test for Syphilis Charles R. Rein, Louise C. Kelcec, G D Alessandro and J H De Bruijn[3] (New York Univ Post Grad Med. School and Skin and Cancer Unit) studied 1 055 serum specimens with complement fixation tests using pathogenic Treponema pallidum and nonpathogenic Reiter treponeme protein extract antigens. The one-fifth volume Kolmer and the Kent 50% end point complement fixation technics were used The antigen titrations were 1 80 with the former and 1 250 with the latter Comparative studies with the two technics on identical specimens indicated that the results obtained with the Kent 50% end point technic were more reproducible and easier to read with elimination of many anticomplementary and partial anticomplementary reactions The level of sensitivity was comparable with the results obtained with the one-fifth volume Kolmer technic.

Sensitivity was evaluated in 206 patients with treated early late and latent syphilis. The results showed a level of reactivity comparable with that obtained with the T pallidum immobilization (TPI) T pallidum immune adherence (TPIA) and T pallidum complement fixation (TPCF) tests. Specificity was evaluated in 99 nonsyphilitic seropositive patients. The results showed a degree of specificity equal to that obtained with the TPI TPIA and TPCF tests

► [The first one of the newer highly specific tests for syphilis which is relatively simple to perform and not too expensive for extensive use.—Eds]

Reiter Protein Complement Fixation Test for Syphilis. George R. Cannefax and Warfield Garson[4] (Univ of North Carolina) compared the results obtained with the Reiter protein complement fixation test (RPCF) the Treponema pallidum immobilization test (TPI) and the T pallidum complement fixation test (TPCF) on 765 syphilitic and 615 presumably nonsyphilitic serums The Reiter protein antigen was prepared by the method described by D Alessandro and Dardanoni except the precipitate was put into solution and dialyzed against saline solution whereas phosphate buf

(3) J Invest. Dermat. 28 459 462, June 1957
(4) Pub. Health Rep 72 335 340, April, 1957

fer was used in the original method and whereas merthiolate was used in th original method as a preservative, no preservative was used in the antigen prepared for the present experiments

The TPI test showed the lowest percentage of positive results in cases of primary and secondary syphilis, 25.7 and 72.7 as compared with 62.9 and 89.7 for the TPCF and 61.4 and 84.6 for the RPCF test. This difference, which probably occurs because the TPI antibody appears later in the course of the nfection than do the other antibodies, accounts in great measure for the generally lower sensitivity of the TPI test. With all diagnostic groups of syphilis combined, the positivity rates were 75.4% for the TPI 82.6% for the RPCF and 86.8% for the TPCF test.

The 615 presumably nonsyphilitic serum specimens used for determination of relative specificity of the RPCF test ga e negative results to the TPI and TPCF tests n a serologic survey in an area with a high incidence of syphilis With the RPCF test, pos tive results in some degree were obtained with 14 serums, indicating specificity of 97.72% n elation to the TPI and TPCF tests. Clinical informa tion subsequently obtai ed on 10 of the 14 patients revealed that 7 had had previous treatment for syphilis If these 7 are excluded, the specificity of the RPCF tests becomes 98.86%.

It has become a serologic axiom that tests using Reiter s treponeme produce a high percentage of false positive reac tions. In this preliminary in estigation a protein fraction of Reiter s organism (presumably free from lipid antigen substance which reacts with reagin) did not produce a high percentage of false positive reactions when compared with the TPI and TPCF tests.

► [These favorable results achieved with the Reiter protein antigen prepared by the method of D'Alessandro and Dardanoni are entirely in agreement with those obtained in our laboratories by the late Charles Rein, George Kostant and Louise Kelcec.—Eds.]

Treponema Pallidum Immune Adherence (TPIA) Test in Diagnosis of Syphilis s compared with the T pallidum immobilization test (TPI) by James N Miller Ruth Book and Charles M Carpenter[1] (Univ of California, Los Angeles) using standard procedures and suitable controls. In the TPIA test, treponemes not adhering to the surface of the red blood cells remained free in th supernatant flu d, which was

(1) J A M A. 143 113 114, Jan. 12, 1957

examined on a dark field microscope. The number of treponemes taken in 20 fields at random was recorded. The percentage disappearance of treponemes from the supernatant fluid was calculated. The test was considered positive if the degree of disappearance was 50% or greater inconclusive if from 26 to 49% and negative if less than 26%

Preliminary TPIA tests on 21 positive and 20 negative serum samples showed perfect correlation with the TPI tests The sensitivity was demonstrated on the serums of 25 patients who had been treated and who had a positive serologic test for syphilis (STS) and on 44 serums from patients with a reactive STS but with no history of the disease. The TPIA test was positive in 22 of group I whereas the TPI test was positive in only 20 In group II all the serums showed positive reactions to both tests. Tests on the specificity of the TPIA tests with 26 normal serum samples showed perfect correlation with the TPI tests Of the 53 samples from persons with a reactive STS but no history of the disease, 52 were also in agreement. Only 1 negative TPI was positive on the TPIA test For specificity the correlations of the two groups were 100 and 97%

The TPIA test was shown to be superior in tests for sensitivity and equivalent in tests for specificity The TPIA test has several advantages Considerable antigen may be prepared and stored because heat killed treponemes are used and a colony of rabbits is not required The antigen for the TPIA test is stable for at least 6 months Only 5 hours are required for the TPIA test but 2 days for the TPI test. The TPIA antigen is less expensive than the TPI antigen Anaerobic facilities necessary to maintain the motility of T pallidum in the TPI tests are not required in the TPIA test. The TPIA test may also be used to detect biologic false positive reactions for syphilis The TPIA test requires further comparative tests in several laboratories.

Complement Titer and Complement Fixation Test with Treponema Pallidum. In recent years attempts have been made to work out further serologic reactions which would supplement the T pallidum immobilizing (TPI) test However the T pallidum immune adherence test (TPIA) though satisfactory is rather complicated since agglutination reaction with T pallidum contains nonspecific agglutinins that reduce the practical value of this reaction Com

plement fixation reactions with culture spirochetes (Reiter) are not antibody reactions to syphilis. Kurt Meinicke[4] (Univ of Munich) eports experiments based on complement titer and complement fixation reactions with dead T pallida.

It was found that TPI tests cannot be carried out without active complement. The author's experiments revealed that exact complement titrations before and after the TPI test permit checking the results of specific immobilization. Treponema suspension, serum and complement were mixed and the complement titer ascertained by addition of hemolytic system. The last test tube of the dilution series with complete hemolysis i dicated the titer value. In positive se rums, an average complement titer diminution of 8-10 units usually occurred after tubes had been incubated at 35 C. for 18 hours. In negati e serums, complement diminution was between 2 and 4 units only Despite the comparatively simple technic, complement titer reaction cannot be used presently because of the required material and time.

The T pallidum complement fixation reaction with dead T pallida is difficult because preparation of the antigen is, as expected, extremely difficult. Serum dilutions ant gen suspension and complement were mixed in test tubes and kept for 30 minutes at 4-6 C in the refrigerator Later they were kept in a water bath at 37 C. for 30 minutes and 0.5 cc. of the hemolytic system was added to the test tubes which were again kept for 30 minutes in a water bath of 37 C.

Comparative tests of T pallidum complement fixation reaction, culture spirochetes (Reiter) antigen reaction Mein icke reaction II and TPI test showed marked parallelism between T pall dum complement fixation reaction and TPI test. Nonspecific esults with spirochetes (Reiter) reaction and Meinicke reaction II were disclosed by T pallidum complement fixation reaction as well as by TPI tests although the former reaction seems to be less sensitive than the TPI test. Because of the existing obstacles and difficulties in preparing the antigen, T pallidum complement fixation reac tion cannot be used for testing in a large series, but like com plement titer eaction adds much to the serology of syph lis

It is concluded that the TPIA test, agglutination reaction and T pallidum complement fixation reaction cannot be used for routine testing in the same way as the TPI test.

(4) Hautarzt 7-540-543, December 1954.

9 OTHER INVESTIGATIVE STUDIES

5 Hydroxytryptamine and the Skin. According to G B West and J R. Parratt[7] (Univ of London) 5-hydroxytryptamine (5-HT) is an amine related to and probably derived from the amino acid tryptophan It has been found in all tissues containing cells belonging to the enterochromaffin system in the blood in the spleen and in some central nervous structures The physiologic significance of this amine remains unsolved though many possibilities exist. It may influence hemostasis or control vascular tone and therefore the systemic blood pressure It may participate in regulation of kidney function or in brain function Recently it has been associated with tissue mast cells in the skin of the rat

Great variation was found in the 5-HT content of the skin of various species Large quantities were noted only in the rat Mouse skin showed a significant amount of 5-HT but human skin did not In the mouse cutaneous 5-HT bears a relation to the histamine and mast cell contents of separated layers of the skin whereas in the rat the highest amounts were found in areas poor in mast cells and relatively poor in histamine These findings suggest that in the skin of the rat tissue mast cells are not the only source of 5-HT hence other tissue components may have the faculty for storing this compound. Reserpine caused pronounced depletion of the 5-HT stores in the skin and elsewhere but had little or no action on histamine stores

Specimens of human skin from a patient with urticaria pigmentosa and from a mast cell tumor did not show increased 5-HT levels The 5-HT value in a biopsy specimen of human skin from a patient with argentaffinoma was not increased. It is not known whether patients with allergic disorders possess raised 5 HT levels of the skin

When rats were given 50% native egg white intraperitoneally edema of the skin of the extremities occurred. To test whether 5-HT is essential for production of edema rats were given compound 48/80 to disrupt the mast cells of the skin and deplete the histamine and 5-HT levels When they were

(7) A.M.A. Arch. Dermat. 76 336-342 September 1957

exposed to egg white no edema resulted, and assays indicated that no histamine or 5-HT had been released by the egg white. When rats were first treated with reserpine again no edema occurred after injection of egg white though histamine was still released. It is clear therefore that 5-HT is needed to produce edema by egg white Histamine must play a part but the more important amine is 5-HT which is about 200 times as activ as histam ne in producing this local vascular injury

There is no doubt that 5-HT now takes its place alongside histamine as a possible mediator of the response to inflammation o injury in certain s tes of the body of th rat. Whether this hypothes s is correct in tissues such as human skin deficient in 5-HT is not known. In man t may be that 5-HT s too toxic to the sensory organs in the kin for it to remain there

► [There already is convincing evidence that 5-hydroxytryptamine plays an important role in certain cutaneous reactions in some species of animals. However as shown in this summary conditions ar extremely complicated, but ith variations in the 5-HT content in the several parts of the skin and in the different species. W ould like to call ttention to the fact that (1) 5-HT has been shown to play significant metabolic role in the human brain. (2) 5-HT and nicotinic acid are derived from tryptophan, and excess production of 5-HT apparently may lead to deficiency in nicotinic acid and (3) reserpine, hich has been show by Schnyder and Storck to have some effect on allergic contact sensitization, causes depletion in 5-HT in the brain and in the skin. Evidently it is not necessarily through its cerebral action that reserpine has its effect on allergic contact sensitization in animals.—Eds.]

Role of Histamine and of Serotonin (5-Hydroxytryptamine) in Pathogenesis of Increased Permeability of Cutaneous Capillaries of Anaphylactic Origin. Cutaneous pass ve anaphylaxis n guinea pigs and rats corresponds to the urticarial wheal in human skin. This reaction can be blocked by antihistamines and s mulated by intradermal injection of histamine Certain experiments indicate that histamine i not the sol intermediary and 5-hydroxytryptamine (5-HT) has been dentified as also nvol ed in the cutaneous reaction Theodor Inderbitz n and Lucien Craps (Univ of Zurich) report experiments to determine elative amounts of histamine d 5-HT liberated in the skin at the s te of reaction and their significance with egard to local circulatory d sturbances of anaphylactic origin.

Studies on amounts of histamine 5-HT and mastocytes at the site of skin reactions showed a moderate decrease in his-

(I) Dermatologica 1 200 314, Mar Apr 1957

tamine (never over 30% of initial content) at the center of intensity of the anaphylactic reaction. Methods used did not demonstrate liberation of 5-HT during the cutaneous anaphylactic reaction Numerical diminution of mastocytes is inappreciable, according with moderate loss of histamine, the morphologic substrate of which is a partial discrete and diffuse mastocytic degranulation not affecting the number of cells

Injection of substances increasing capillary permeability stimulates development of an inflamed homogeneous plaque about 4-5 mm in diameter for the minimal active dose. Then the diameter undergoes linear increase with respect to logarithm of dose to 10-11 mm which is not exceeded. With higher doses the lesion is modified a ring is produced with the center slowly inflamed With further increase capillary spasm persists at the injection site and only the periphery is inflamed.

With histamine the diameter of the lesion increases parallel to logarithm of dose varying from 0 02 to 0.3 μg Premedication with a 5-HT antagonist is without effect, but an antihistamine inhibits 250 times the minimal and 64 times the maximal dose Addition of a 5 HT antagonist does not modify the antihistaminic effect.

By weight 5-HT is 4 times more active than histamine (expressed in 5-HT-creatinine sulfate) An antihistamine causes moderate depression (4 times) only for the maximal surface dose An antagonist of 5-HT inhibits 4 000 times the minimal and 1 000 times the maximal dose. Addition of an antihistamine is without effect.

With compound 48/80 (product of condensation of p-methoxyphenethyl methylamine with formaldehyde) in normal animals active initial minimal dose is 0 06 μg and that producing a lesion of maximal surface 1 μg A 5 HT antagonist inhibits 4 times the minimal dose without influencing the maximal surface dose Antihistamine inhibits these reactions 16 times Combined premedication exerts a constant cumulative effect carrying inhibition of minimal dose to 256 times and of maximal dose to 64 times Mastocytic degranulation is proportional to dose of 48/80 It predominates at injection site where mastocytes are greatly diminished or nil whereas normal conditions are gradually approached toward the region of the periphery This is in

contrast with the homogeneity of the anaphylactic lesion Vascular response to the anaphylactic stimulus (crystalline ovalbumin) appears with the same delay as augmentation of capillary permeability with the above substances after 30 minutes, the lesion is fully developed. The lesions are larger reaching 7 17 mm. for minimal and maximal doses of antibody of 20 and 80 μg because of intradermal diffusion of antibody from its injection to release of reaction by intravenous antigen. (This delay of fixation is necessary to avoid nonspecific vascular reactions) Within these limits, size of the lesion is proportional to intensity of reaction. It is not influenced by antihistaminic premedication or 5-HT antagonist, simple or combined.

The authors conclude that the cutaneous passive allergic reaction liberates histamine and probably 5-HT from mastocytes. Liberation of 5-HT although quantities are too small to be directly demonstrable is rendered likely by the fact that this occurs in other conditions in which mastocytes also release histamine. Liberation of 5-HT should not exceed 30% of cutaneous content which corresponds to the maximal quantity of histamine released. The antigen-antibody stimulus, at least in the skin is a moderate liberator of histamine, less efficient than simple trauma, such as refrigeration.

Histamine and 5-HT injected into the dermis or released locally by mastocytes stimulate an increase of capillary permeability which is specifically inhibited by their antagonists, each alone or combined. Combined use of these antagonists does not affect increase of cutaneous capillary permeability of allergic origin Hence histamine and 5-HT liberated in passive cutaneous allergy are not solely responsible for the increased capillary permeability and consequent edema

Chromaffin Granules and Their Cellular Location in Human Skin. In a series of biopsies from human skin Hans Nordenstam and Jack Adams-Ray[4] (Serafimer Hosp Stockholm) demonstrated chromaffin granules by several approved histotorial methods The modified Sevki method was superior visualizing larger numbers of granules with excellent contrast between the red chromaffin structures and surrounding tissues. The cells containing chromaffin granules have a characteristic appearance. The granules occur in long snakelike protrusions of cytoplasm, with pale elongated nuclei en

(4) Ztschr Zellforsch 5 435-443, 1957

cased in a narrow zone of granulated cytoplasm. The protrusions are usually bipolar but may be unipolar branched or show terminal swellings

The chromaffin cells are irregularly distributed through the corium being more numerous around vessels, nerve fibers sebaceous glands and hair follicles The superior part of the corium contains a larger number of cells than the deeper part and subcutaneous tissue. Skin from the calf contained 2–4 times as many cells as skin from the abdomen. In skin from the calf considerable reduction in chromaffin granules and typical cells was noted 24 hours after death Autolytic changes were noted especially in the cytoplasmic protrusions

Though the granules of mast cells simulate chromaffin granules in preparations stained by the modified Seki method the characteristic morphology of the chromaffin cells usually makes differentiation possible In the gastric wall, where both types occur rather abundantly the Ziehl-Neelsen stain is helpful A curtailed variation with carbol fuchsin but without subsequent counterstaining with methylene blue gives to the acid fast granules of the mast cells a dark red or bluish color resisting even long differentiation with hydrochloric acid alcohol Treated in the same manner the chromaffin granules are brownish red and slightly resistant to differentiation disappearing before the mast cell granules have begun to decolorize Mast cells also differ from chromaffin cells in that the granules are not argentaffin do not reduce ferriferricyanide and lack yellow autofluorescence in ultraviolet light Mast cell granules are larger than chromaffin granules and mast cells are considerably larger than most chromaffin cells The nuclear structure and general shape of mast cells differ considerably from those of chromaffin cells

Demonstration of noradrenaline and adrenaline was successful in human skin in skin from a cat and from rats but not in the mesentery of rats The identity with chromaffin granules could be established in most instances

Liberation of Endogenous Histamine in Man was studied by J Lecomte[1] (Univ of Liége) A potent histamine liberator L 1935 was given intravenously to 40 patients none of whom had allergic disease Slight reactions, consisting of

(1) J Allergy 28 102 112, March 1957

a sensation of heat in the head, pricking of the skin of the face and erythema of the face and neck with no change in the pulse rate and blood pressure followed rapid intravenous injection of 0.1 mg./kg. With injection of 0.3 mg./kg. itching of the face occurred within 30-40 seconds at the same time, there was a sensation of heat in the head. Itching then spread to the palms and upper chest and after 1 2 minutes the skin of the face became red. Vasodilatation extended to the shoulders and sides of the trunk. The pulse became more rapid and the blood pressure dropped 20-40 mm. Hg. Erythema and fall in blood pressure persisted for about 15 minutes.

After injection of 0.5 mg./kg. 11 patients had serious reactions. Itching of the face was accompanied by intense cephalic heat. Erythema appeared first on the face, then spread to the chest, abdomen and groins. Itching became intense and spread to the whole skin surface. The pulse became rapid and blood pressure fell sharply. Vomiting occurred, with a feeling of imminent defecation and agonizing bradypnea. After 10 minutes, the reaction began to subside. Urticaria appeared and persisted for a variable time.

Two patients had severe reactions after intravenous injection of 0.5 mg./kg. becoming dyspneic, cyanotic and pale. There was sudden fall of blood pressure and acceleration of the pulse. Symptoms were relieved promptly by intravenous administration of 60 mg. Sympatol.*

These reactions which resulted from liberation of endogenous histamine became milder with successive injections of L 1935 as available stocks of histamine in the tissues were depleted. Previous injection of antihistamines modified or prevented the reactions. At the climax of the fall in blood pressure during a severe reaction plasma histamine was doubled.

Anaphylactic shock manifests itself in man by symptoms analogous to those provoked by release of endogenous histamine. Lecomte suggests, therefore, that anaphylactic shock is due to endogenous histamine release.

* [It is true that anaphylactoid reactions in man are manifested by some of the same symptoms as those produced by the histamine liberator. On the other hand, some of the symptoms caused by the histamine liberator are missing in allergic and anaphylactoid reactions.—Eds.]

Use of New Histamine-Liberating Substance, Compound 48/80, in Human Subjects. The effect of various known his-

tamine liberators varies greatly in different species of animals and different organs, but in most cases a new compound, 48/80 has proved to be the most potent of the group. After injection of 48/80 a granular depletion of the mast cells can be observed histologically. Intracutaneous injection produces a wheal similar to that observed after histamine injection.

Nils Brage Nordlander[2] (Univ. of Uppsala) administered 48/80 to about 110 patients. Usually it was given intravenously but sometimes intramuscularly. First 10-100 µg was given at intervals of 1 to several days. If no side effects were noted, dosage was increased to 1-6 mg. Individual tolerance varies greatly and increases with repeated doses. The injection was given slowly and was usually stopped when the patient felt a burning or pricking sensation in the skin. The first sensations are usually felt in the scalp, on the forehead and around the ears. The feeling then spreads to the upper part of the trunk and palms and sometimes to the abdomen and upper thighs. In a few moments erythema of variable intensity appears. If the injection is interrupted immediately all symptoms disappear in 5-10 minutes. If the injection is continued, the flush may remain for 30 minutes or more and with larger doses urticarial wheals can be produced.

With small doses there is no change in blood pressure, but with larger amounts a moderate drop is noted. Some patients have a peculiar sensation of tiredness and numbness in the calves resembling the paresthesia observed in "restless legs."

Improvement was marked in a woman with Besnier's prurigo since childhood. The first few injections of 48/80 were followed by considerable clearing of the eczema, but a flare-up occurred when she was unable to receive treatment because of a cold. Marked improvement was again noted after the first injection and improvement continued with subsequent treatment. Similar response to therapy had been observed in the past only with ACTH.

Studies on Chronic Local Anaphylactic Reaction in Rabbit Ears. I. Macroscopic Changes Produced by Long Term, Iterated Injection of Bovine Serum Albumin into Same Skin Area are described by Stig Hård[3] (Karolinska Hosp., Stockholm). Characteristic of the reaction were hyperemia, edema, loss of hair, hyperkeratosis, crusts, glossy skin, hyperpig

(2) Acta med. scandinav. 157: 235-240, 1957.
(3) Acta dermat.-venereol. 36: 303-334, 1956.

mentation, depigmentation, atrophy diffuse papillomatosis and solitary papillomas.

The inner aspect of rabbits ears was used 1 ml. of 1% sterile bovine serum was injected every 3 or 4 days into the upper dermis in 26 rabbits From 14 to 80 injections were given The highly anaphylactic stage was reached after the 7th injection, 24 days from the start of sensitization. Edema and erythema (particularly follicular) were prominent.

Topical hydrocortisone therapy inhibited the reactive processes, such as hyperemia infiltration and hyperkeratosis despite continued albumin injections. If injections extended through the highly anaphylactic period into the stage of abating anaphylaxis, the acute dermatitis subsided and necrosis followed If the local reaction became severe, vesicles and bullae were seen. After a long period of injection with the antigen, the proliferative phenomena abated, i.e., the skin ceased to react with hyperplasia if the antigen was injected sufficiently long into a constant skin area.

Comparison is made between the chronic local anaphylactic reaction and the local adaptation syndrome of Selye. There is the local alarm reaction as anaphylaxis increases there is the local stage of resistance characterized by hyperplasia in the highly anaphylactic stage and finally there is the local stage of exhaustion in the period of abating anaphylaxis.

Many of the pathologic skin changes in the chronic anaphylactic reaction are similar to certain dermatoses, especially eczema. Therefore chronic local anaphylactic reactions may be used to study the general and local effects of various substances on the pathologically altered skin

[It is quite remarkable that Hürd was able to produce blistering in rabbits skin with such relative ease Vesiculation on unaltered rabbits skin is extremely rare, not to say almost unknown. Unfortunately the original article does not contain reproductions of the histologic changes in the rabbits skin. It could have been instructive to know whether the skin in which the vesiculation occurred was markedly acanthotic. As has been shown by Baer Rosenthal and Sims (p. 452) thickening of the prickle cell layer which is normally very thin, produces capacity to react with histologically demonstrable vesiculation in the skin of guinea pigs. In no instance, however were blisters seen macroscopically in such guinea pigs.—Eds.]

Cutaneous Anaphylaxis and Proteolysis. Lucien Crapa and Theodor Inderbitzin (Univ of Zurich) report experiments on rats and guinea pigs which included determinations of histamine and 5-hydroxytryptamine (5-HT) in skin subjected to proteolysis (trypsin, streptokinase) and passive

(9) Dermatologica 114 ZZZ ZZ1, Mar-Apr 1957

anaphylactic reactions increase of permeability of skin capillaries in these two types of reaction and a comparative histologic study of proteolytic and anaphylactic lesions.

In both species there is prompt moderate decrease of histamine in skin subjected to proteolysis. Its latency and intensity corresponds with that of a cutaneous anaphylactic reaction Variations in 5-HT could not be demonstrated in the anaphylactic lesion or after injection of proteolytic enzymes

Diameters of lesions obtained after injection of proteolytic enzymes increase linearly between two limits, i e. the threshold of effect on capillary permeability and maximal size of the lesion With higher doses the homogeneous plaque is replaced by an inflamed ring Premedication of animals with histamine antagonists (50 mg pyrilamine maleate/kg intraperitoneally 50 minutes before) and with 5-HT antagonists (4 mg BOL 148/kg) alone or combined does not influence the diameter of the lesions Inactive proteolytic ferments are without effect Hence proteolysis or intermediaries which it liberates or produces in the skin cause the increase of capillary permeability and histamine and 5-HT evidently are not the most important of these as their inactivation remains without effect Here again the situation is analogous to changes in capillary permeability characterizing the anti body antigen effect

Injection of active proteolytic ferments reproduces histologic appearance of anaphylactic cutaneous reactions When quantities of antibody or antigen are small reaction is limited to interstitial dermal edema, with discrete leukocytic extravasation disappearing without sequelae in some hours (urticarial reaction) If amounts are greater the Arthus phenomenon is observed to edema is added an inflammatory cellular infiltrate composed mainly of polymorphonuclear neutrophils Dilated capillaries are filled with leukocytes When edema represses in 3-48 hours depending on its intensity polymorphonuclear inflammation develops during the first 6 hours and then is replaced progressively by monocytic elements constituting a nonspecific granuloma of resorption Instead of being rapidly resorbed the lesion becomes indurated and may finally be necrosed

Very dilute proteolytic solutions also produce capillary vasodilatation and transient edema When more concen

trated, they provoke an inflammatory leukocytic afflux. If proteolytic activity is still further increased, the lesion is hemorrhagic. Since trypsin in large doses destroys tis ues, anaphylactic lesions of maximal intensity cannot be produced, and average reactions developing in 4 hours are not precisely imitated because the specific inflammatory phase develops more rapidly at the 5th hou edema is usually already resorbed. Polymorphonuclear inflammation is also reduced, and the ring of leukocytes surrounds vascular walls and is less dense Con ersely injection of large doses of streptokinase (2,000-5,000 units) stimulates marked edema of prolonged evolution rich in leukocytes. At higher doses, the lesion is hemorrhagic.

When the action by proteolysis is sufficiently severe, the secondary phase of resorption is in all ways similar to that of anaphylactic cutaneous lesions. This secondary phase can also be produced by injecting a sufficient quantity of inactive ferments but they do not induce the immediate specific response of vasodilatation edema and polymorphonuclear in filtration

Whatever the quantity of enzyme injected, mastocytic in volvement remains discrete and diffuse appreciable only by systematic count of cells in serial sections. Its intensity is not comparable to that caused by cutaneous refrigeration or parenteral o local injection of compound 48/80 Diminution of number of mastocytes is also homogeneous, as in cu taneous anaphylactic reactions.

These facts support the proteolytic theory of anaphylaxis (first proposed by Jobl ng and Petersen in 1914 and revived in 1953) and would seem to justify its extension to localized anaphylactic man festations as well as anaphylactic shock. Present experiments do not permit conclusions as to whether the enzyme has a d rect toxic effect on the vascular system or esults from elaboration of polypeptides at the ex pense f tissue proteins or whether both these mechanisms operat simultaneously

Proteolytic Activity in Dermatoses Preliminary Observations on Inflammation and Pruritus. Until recently t was thought that itching was mediated largely by histamine Se ere itching occurs commonly in clinically normal skin. Conversely itching from histamine always is accompanied by visible reaction This discrepancy led Shelley and Arthur

to investigate itching produced by cowhage. They found that a proteolytic enzyme extracted from cowhage spicules produced itching without visible reaction and that other proteinases of animal and vegetable origin also produced itching on injection.

Frank E. Cormia John W Dougherty and Shirley A. Unrau[5] (New York Hosp -Cornell Univ Med. Center) report that intradermal injection of fibrinolysin or crystalline trypsin in uninvolved skin of patients with atopic dermatitis erythroderma urticaria pemphigus and dermatophytosis often aggravated the existing dermatosis. Intradermal injection of trypsin aggravated the pre-existing triple response of Lewis and reactivated a quiescent one. Itching was produced regularly by intradermal injection of streptokinase profibrinolysin fibrinolysin, trypsin, ficin and papain thus confirming the studies of Shelley and Arthur Itching could not be produced with moccasin snake venom

Itching occurred 1 3 seconds after intradermal injection of histamine With trypsin the interval averaged 16 seconds, with fibrinolysin 19 seconds with profibrinolysin 21 seconds and with streptokinase 3 7 minutes. These results indicate roughly the time necessary to complete the various phases of the proteolytic cycle. The itch response to proteolytic enzymes in patients with dermatitis varied greatly from that in normal controls The time sequence for development of itching after intradermal injections of streptokinase, profibrinolysin, fibrinolysin and histamine indicates that the mechanisms involved in pruritus are similar to those of inflammation Patients with localized pruritus tended to be hypersensitive, whereas those with extensive severe itching usually were hyposensitive or nonreactive.

Use of trypsin for determining threshold itch was less reliable than when histamine was used. Itching after injection of a protease often preceded the visible histamine response. When the itch response to histamine in a local cutaneous site was exhausted by repeated injections of histamine, itching or burning could still be produced by local injection of a proteolytic enzyme

Itching scattered over the body and lasting 1 3 hours often was produced by injection of streptokinase fibrinolysin and trypsin Initiation of prolonged itching in scattered areas

(5) J. Invest. Dermat. 28 425-433 June, 1957

after intradermal injection of relatively small amounts of a proteolytic enzyme suggests that itching, once started tends to perpetuate itself for variable periods. In patients in whom itching develops, there may be sustained release of enzyme through continued activation or inadequate inhibitor mechanism. In any event, itching with or without dermatitis leads to scratching superimposed dermatitis and infection. Scratching presumably releases epidermal cathepsins, superimposed dermatitis may be associated with increased fibrinolytic activity and secondary infection results in liberation of bacterial kinases. Leukoprotease released by destruction of leukocytes also may be important. It is probable that this produces further tissue injury and more release of proteolytic enzymes. Thus the cycle may be perpetuated, even after the precipitating cause has been removed.

► [Patients with severe widespread itching usually are highly susceptible to even the mildest itch stimulation from fibers in clothing, air currents, etc. It therefore comes as surprise that patients with extensive severe itching usually are hyposensitive or nonreactive to the itch-stimulating action of the proteolytic enzymes.—Eds.]

Distribution of Alkaline Phosphatase in Normal and Pathologic Human Skin. Alfred W Kopf[4] (New York Univ Post Grad. Med. School and Skin and Cancer Unit) demonstrated alkaline phosphatase in 29 normal and 224 pathologic skin specimens, using a modification of the Gomori Takamatsu technic. The optimal incubation period was 4 hours Strong false positive precipitates were found in the inner root sheath of hair follicles and soft keratin. A light false positive deposit was seen on keratohyalin granules of the stratum granulosum, degenerated elastica colloid and in the hair medulla

In normal human skin marked alkaline phosphatase activity was observed in hair papillae, moderate activity in capillaries, eccrine sweat glands and the external connective tissue sheaths of hair follicles, mild activity in hair bulb matrix cells and apocrine sweat glands and weak activity in subcutaneous fat trabeculae. No demonstrable activity was present in any epidermal strata, collagen and elastica, any elements of the follicular apparatus except those mentioned before eccrine and apocrine ducts, sebaceous glands (with rare exceptions of weak activity in peripheral cells) nerves and smooth muscle

In pathologic skin early stages of vascular proliferation,

(4) A.M.A. Arch. Dermat. 75:1 17 January 1957

e.g. hemangiomas, granulomas, inflammatory dermatoses and angiosarcomas, etc., showed marked alkaline phosphatase activity; later stages showed reduced or no activity. Banal cellular infiltrates associated with acute inflammatory dermatoses often displayed moderate to marked activity, whereas the cellular components of chronic inflammatory conditions frequently showed little or no activity. Pure epithelioid and reticuloendothelial proliferations generally showed no alkaline phosphatase activity.

Early phases of connective tissue proliferation, e.g. cutaneous nodule, keloid and scar tissue, showed moderate to marked alkaline phosphatase activity, whereas late stages showed little or no activity. Benign neoplasms often showed an activity similar to that of the tissue from which they originated. Malignant neoplasms showed variable activity. Prickle cell epithelioma and malignant melanoma showed no phosphatase activity of the malignant cells themselves, but about 30% of basal cell epitheliomas showed activity in relation to the tumor cells. Kaposi's sarcoma showed intense activity.

In general, alkaline phosphatase is demonstrable at sites of high metabolic activity in normal and diseased skin. Therefore, diseases manifesting active proliferation frequently show increased alkaline phosphatase activity. Proliferating elements of tissues which in normal skin contain no significant quantities of enzyme usually show measures of activity in pathologic lesions, e.g., the alkaline phosphatase activity seen in sebaceous adenoma and lipoma. Exceptions occur, however, as in prickle cell epithelioma and epithelioid hyperplasias. The precise role played by alkaline phosphatase in cutaneous metabolic processes remains obscure.

Alkaline Phosphatase in Alopecia Areata. Alkaline phosphatase, an enzyme which acts as an organic catalyst in a wide variety of biochemical processes in metabolism, is concerned with transmembranous solute transfer, calcification and ossification, fibroplasia, histodifferentiation, inflammatory reaction and glandular secretion. Yet the precise role it plays in cutaneous metabolic processes remains obscure. Alfred W. Kopf and Norman Orentreich[7] (New York Univ. Post Grad. Med. School and Skin and Cancer Unit) report further studies of its activity in alopecia areata.

(7) A.M.A. Arch. Dermat. 76:288-295, September, 1957.

In normal scalp biopsy specimens, the papillae of anagen (growing phase) follicles giving rise to terminal hair invariably have mild to intense degrees of histochemically demonstrable alkaline phosphatase act vity This acti ity is diminished or absent in the hair papillae during the early stage of alopecia areata. In the intermediate stage as the follicles atrophy alkaline phosphatase activity of the hair papillae is restored. Late stages of alopecia areata and totalis show arrested miniature follicles situated in the upper cutis. These tiny usually non-hair producing pilar epithelial columns have intense alkaline phosphatase activity of their papillae.

Local njection of hydrocortisone into sites of alopecia areata and totalis can produce regrowth of terminal hair These follicles in the early stages of differentiation and hair production have strong alkaline phosphatase activity of their papillae. The enzymatic activity gradually diminishes as the folli les mature The role alkaline phosphatase plays in this transformation of miniature follicles of alopecia areata into anagen follicles is unknown, but the intense activity of this enzyme in the early stages of regrowth ndicates that rapid proliferation of the follicle cells requires the presence of large quantities of active alkaline phosphatase. Since it has been demonstrated that all structures n early phases of histodifferentiation are associated with high degrees of alkaline phosphatase activity the strong enzyme activity during early phases of histodifferentiation in ha r regrowth may be explained by the apparent prerequisite for alkaline phosphatase by tissues during their developmental stages.

The cause of partial or complete loss of alkaline phosphatase activity n th early stages of alopecia areata is not known Theoretically it could be the direct cause of the alopecia, but more lik ly t only one of the many biochemical alterations wh h occur when hai growth ceases in this disease Many chemical and a few physical agents are known to inhibit the act v ty of this enzyme. None of these agents ha been accepted as causative in alopecia areata It has been suggested that a slowly diffus ble substance is formed by the inner root sheath of the hair foll cle which is a regulatory factor n cy lic hair growth. It is conceivable that such a substance act a a enzyme nhibitor and ts continued over production could be causative in this disease

Histochemical Demonstration of Cholesterinases in Vegetative Nervous System of Skin The distal part of efferent nerve fibers in the skin consists of a syncytium, a three-dimensional protoplasmic network containing nuclei, vacuoles argyrophilic granules and neurofibrils in varying amounts and arrangement. This terminal nervous syncytium which in toto represents a nerve ending can respond to nervous stimulation of postganglionic nerve fibers with the formation of one single humoral transmitting substance. By diffusion into interstitial spaces, this substance acts on nonnervous elements (glandular cells, smooth muscle fibers and blood vessels) and is assumed to be adrenergic in nature (Jabonero) because it can easily be demonstrated by osmium-iodide mixtures Cholinergic elements on the other hand, cannot be demonstrated directly because no histochemical method exists to evidence the easily diffusible acetylcholine. Attempts were made to show cholinergic innervation indirectly i e by demonstration of the specific acetylcholine splitting enzyme the specific cholinesterase or acetylcholinesterase

Because there was no conformity of results obtained by various investigators W Thies and L. F Galente[8] (Univ of Munich) studied cholinesterase distribution in human skin using a modified method of Koelle and the silver carbonate method of Jabonero The former rather complicated procedure shows cholinesterase as very fine dark brown granules the latter serves as a control of histochemical findings.

Specific cholinesterase activity was highest around the tubules of eccrine sweat glands and in the smooth muscle fibers of the nipple and arrectores pilorum muscles showing densely crowded fine dark brown granules on the surface of vegetative plasma strands These findings corresponded to those obtained by silver impregnation Arrectores pilorum muscles also displayed a diffuse brownish hue probably due to the presence of nonspecific cholinesterase (acetylthiocholine is split faster by specific and butyrilthiocholine by nonspecific cholinesterase) Specific cholinesterase was scarcely showing in a few plexus strands in the apocrine glands and almost completely missing within the perivascular plexus of capillaries in the epidermis and papillary and reticular layers which in silver impregnated section were

(8) Hautarzt 8:69-75 February 1957

rich in vegetative nerve elements In the sebaceous glands specific cholinesterase was absent As to the sensory cerebrospinal nervous system of the skin specific cholinesterase was seen in medullated nerve fibers, in free sensory nerve endings in hair follicles and in terminal bodies. In the latter as in arrectores pilorum muscles nonspecific cholinesterase was also noted.

Findings of abundant specific cholinesterase in the nervous syncytium of eccrine glands not only correspond to those obtained with silver impregnation but also to the response of eccrine glands to parasympathomimetics These facts permit the conclusion that acetylcholine probably acts as a transmitter of nervous impulses. This hypothesis is however hardly compatible with Jabonero s supposition that, in the distant nerve syncytium a single transmitter substance is produced, i e., adrenaline (or sympathin) Provided that in the skin one, not two different, distal syncytia exist it might be assumed that this single syncytium may produce at one time, adrenergic and at another time cholinergic transmitter substance and that the terms adrenergic" and cholinergic" serve only to characterize the predominant, but not the exclusive, transmitting substance.

Histochemistry of Skin Esterases. Gerd Klaus Steigleder and Klaus Schultis[8] (Univ of Frankfurt) nvestigated the effect of various inhibitors and activators of esterases on the azostain-coupling reaction in normal and pathologic skin structures. The technic of Nachlas and Seligman, as modified by Gomori, was used

Biopsy specimens from 60 persons were tested for inhibition and activation Besides normal skin obtained mainly from the finger tips of volunteers, specimens were obtained from persons with necrobiosis lipoidica scar tissue, reticulosarcomatosis, ulcus cruris, mycosis fungoides neurodermatitis diffusa, verruca senilis pityriasis rubra pilaris, histiocytoma, inflammation accompanying phimosis carcinoma spinocellulare carcinoma basocellulare, granuloma annulare psoriasis vulgaris, scar keloids, tuberculosis cutis luposa, sarcoidosis, urticaria pigmentosa, herpes zoster pemphigus vulgaris, cylindroma and chronic dermatitis.

The activating and inhibiting substances were tested in 3 ways (1) the frozen sections were immediately immersed

(8) Arch. klin. u. exper. Dermat. 205:196-211, 1957

for 45 minutes into the aqueous solution of the substance to be tested at room temperature and then transferred into the incubation medium (2) the pretreated sections were washed in water for 15 minutes before incubation and (3) the test substance was added to the incubation medium and the sections were kept there for 45 minutes. The addition of some substances to the incubation medium may influence the coupling before the enzymatic action begins

The following substances were tested sodium taurocholate physostigmine salicylate (Eserine) quinine hydrochloride, sodium fluoride human albumin calcium chloride glycerin Solarson* caffeine citric acid, Irgamide* and Sympatol*

Standard reactions without inhibitors or activators do not allow a new differential diagnostic approach. Especially the histiocytic infiltrations the infiltrations in reticulosarcomatosis and the epithelioid cell infiltrations are similar to each other The infiltrations in reticulosarcomatosis may show different staining intensity Those cells which penetrate into the epidermis and form small abscesses are mostly stained

The esterases in the epidermis differ in their response from the esterases in other organs They are more similar to the esterases of pancreatic than of the liver type inasmuch as they preferably split esters of fatty acids with a long chain. It is noteworthy that the same substances which inhibit the reactions in the epidermis also affect the acetylcholine esterases however it cannot be inferred from this that acetyl choline esterase is present in the skin Certain granulomas, especially those consisting of epithelioid cells and histiocytes react stronger than the epidermis Inhibitors of specific and nonspecific cholinesterase inhibit the esterase reaction in the Meissner bodies in which both cholinesterases are found much more than in the cutis

The esterases of the epithelioid cell and histiocytic infiltrations acted similarly to those of the epidermis, but stained stronger than the latter The strong reaction in the histiocytes epithelioid cells and Langhans giant cells and the similar reaction in the poorly differentiated connective tissue cells in reticulosarcomatosis point to a common origin of these cells Most cells in urticaria pigmentosa of the adult were influenced especially by substances affecting the spe

cific a d nonspecific cholinesterase. The xanthoma cells in hyperlipemic xanthomatous in two b opsy specimens from the same patient were not inhibited by quinine.

Examination of Skin from Patients with Collagen Disease Utilizing Combined Alcian Blue-Periodic Acid-Schiff Stain was made by Edward P Cawley (Univ of Virginia) J F A McManus, Charles H Lupton, Jr (Univ of Alabama) and Clayton E. Wheeler[1] (Univ of Virginia) Current evidence indicates that Alcian blue a relatively new phthalocyanine dyestuff selectively stains structures containing acid mucopolysaccharides. Specimens from normal skin and of in vol ed skin from 6 patients with discoid lupus erythematosus, 4 with disseminated lupus erythematosus 4 with dermatomyositis, 5 with morphea, 4 with generalized scleroderma and 5 with periarteritis nodosa were examined. The com bination stains acid mucopolysaccharides various shades of blue and 1,2-glycols a magenta hue, resulting in excellent color contrast.

Alcian-blue-positive material, in the form of a cobweb-like network of delicate strands that had the characteristics of collagen fibrils, was encountered in the dermis of all speci mens Small quantities of Alcian-blue-positive material were present throughout the upper dermis in discoid lupus erythematosus, in the near vici ity f small vessels of the upper dermis in morphea and generalized scleroderma and through out the upper dermis and n close proximity to damaged ves sels in periarteritis nodosa Small quantities were present throughout the upper dermi in normal skin A salient in crease in Alcian-blue-positive material was found in the upper and m ddle dermis in dermatomyositis and d sseminated lu pus erythematosus, as compared with the other collagen diseases

Mucoid change or myxomatous swelli g of the ground sub stance and fibrinoid alteration of the collagenous tissue are the conspicuous and tangible changes that occur in th ex tracellular components of the connective tissue in th col lagen diseases. Current evidence indicates that mucoid change of the ground substance precedes fibrino d alteration f the collagenous tissue The mucoid change is associated with accumulation of acid mucopolysaccharides. Fibrinoid alteration of collagenous tissu is believed to result from a

(1) J Invest. Dermat. 27:389-394, December 1956.

combination of acid mucopolysaccharides of the ground substance with protein derived from local tissue damage or from the blood

The present studies indicate that acid mucopolysaccharides were present in the dermis of all specimens examined and that they were deposited on or around the collagen fibrils or adsorbed on the collagen fibrils They were greatly increased in cutaneous lesions of dermatomyositis and disseminated lupus erythematosus A suitable explanation for these observations is not available although they may support the concept of a close relation between dermatomyositis and disseminated lupus erythematosus as compared with the other collagen diseases from the standpoint of metabolic alterations in the skin

► [The results of this staining technic, which differentiates between lupus erythematosus and dermatomyositis on the one hand and other so-called collagen diseases such as scleroderma and periarteritis nodosa on the other lend support to the opinion that it is inadvisable at least for the present, to classify all these diseases under the one heading of "collagen disease."—Eds.]

Intermediary Metabolism of Phenylalanine and Tyrosine in Diffuse Collagen Diseases II. Influences of Low Phenylalanine and Tyrosine Diet on Diffuse Collagen Disease Patients were studied by Nagao Nishimura Hisashi Okamoto Masayoshi Hasegawa Shigefumi Nishikawa Yoichi Segawa, Kenzi Hashizume Masataka Yasui Yahito Kotake and Yukio Shibata[2] (Wakayama Med College) The authors previously reported the constant and specific presence of 2,5-dihydroxyphenylpyruvic acid the intermediary metabolite of phenylalanine and tyrosine in the urine of patients with diffuse collagen disease The administration of l tyrosine unfailingly aggravated both the clinical signs of collagen disease and certain laboratory data

Because of these findings 25 patients with diffuse collagen disease were treated with diets low in phenylalanine and tyrosine content They were permitted to have pumpkin onion, radish carrot cabbage coltsfoot [an asteraceous plant—Eds] apple orange tomato strawberry margarine vegetable oil starch and limited amounts of gelatin whale cod and herring Vitamins and tablets containing tryptophan, valine and methionine were also given After 20 days 15 patients with rheumatoid arthritis showed subjective and objective improvement 2 with chronic discoid lupus erythema

(2) Proc. J pan Acad. 33 243-248 1957

tosus showed almost complete clearing and 1 with dermatomyositis had increased grasping power. The edema decreased in 1 patient with diffuse scleroderma and both edema and sclerosis decreased in 1 with acrosclerosis.

In these patients, the tyrosine level in serum mucoprotein dropped remarkably and the creatine and creatinine in the urine decreased, but there was no change in the sedimentation rate.

► [An entirely novel observation, which deserves further investigation. This metabolic error is likely to be a result of the basic pathologic process in lupus erythematosus rather than its cause.—Eds.]

Conversion of Carotene to Vitamin A by Sebaceous Glands. Ruven Greenberg, Theodore Cornbleet and Ronald Demovsky[3] (Chicago) injected a carrot-oil water-solubilized suspension of carotene intradermally. Moderate amounts of vitamin A were demonstrable within 20 minutes of injection in the cells of the sebaceous glands and in the sebum filling the hair follicles and spread on the skin surface. The authors hypothesize that normally there is vitamin A within the sebum but in reduced concentration or in modified form not detectable chemically. Recently, other investigators have shown that vitamin A apparently is involved in glycogen biosynthesis in the liver. If vitamin A is similarly involved in glycogen biosynthesis in the skin, then the functions of glycogen within the skin would be limited when the available concentration of vitamin A was reduced. Normally, glycogen is utilized as an energy source for protein synthesis, for mitosis and for keratinization.

In vitamin A deficiency, the skin is dry, the stratum granulosum is thinned and the stratum corneum is keratinized and thickened. The authors hypothesize that these changes follow subsequent to decreased production of glycogen from small carbon moieties in the sebaceous glands and in the epidermis. Thus the mitotic rate in the cells of the sebaceous glands is reduced and therefore output of sebum by the holocrine glands is reduced. Subsequent to this and because of the reduced supply of vitamin A to the basal cells of the epidermis, their mitotic rate is reduced, but paradoxically there is increased keratinization in all the epidermal structures.

Experimental Investigation of Heparin Effects in Psoriasis was made by Chr. Eberhartinger and F. Reinhardt[4] (Univ. of Vienna). Earlier the authors reported that with

(3) A.M.A. Arch. Dermat. 76:17-22, July, 1957.
(4) Arch. klin. u. exper. Dermat. 203:343-348, 1956.

combination of acid mucopolysaccharides of the ground substance with protein derived from local tissue damage or from the blood

The present studies indicate that acid mucopolysaccharides were present in the dermis of all specimens examined and that they were deposited on or around the collagen fibrils or adsorbed on the collagen fibrils They were greatly increased in cutaneous lesions of dermatomyositis and disseminated lupus erythematosus A suitable explanation for these observations is not available although they may support the concept of a close relation between dermatomyositis and disseminated lupus erythematosus as compared with the other collagen diseases from the standpoint of metabolic alterations in the skin

► [The results of this staining technic, which differentiates between lupus erythematosus and dermatomyositis on the one hand and other so-called collagen diseases such as scleroderma and periarteritis nodosa on the other lend support to the opinion that it is inadvisable, at least for the present, to classify all these diseases under the one heading of "collagen disease. —Eds.]

Intermediary Metabolism of Phenylalanine and Tyrosine in Diffuse Collagen Diseases II Influences of Low Phenylalanine and Tyrosine Diet on Diffuse Collagen Disease Patients were studied by Nagao Nishimura Hisashi Okamoto, Masayoshi Hasegawa Shigefumi Nishikawa, Yoichi Segawa, Kenzi Hashizume Masataka Yasui Yahito Kotake and Yukio Shibata[3] (Wakayama Med College) The authors previously reported the constant and specific presence of 2,5-dihydroxyphenylpyruvic acid the intermediary metabolite of phenylalanine and tyrosine in the urine of patients with diffuse collagen disease The administration of l tyrosine unfailingly aggravated both the clinical signs of collagen disease and certain laboratory data

Because of these findings 25 patients with diffuse collagen disease were treated with diets low in phenylalanine and tyrosine content They were permitted to have pumpkin onion, radish carrot cabbage coltsfoot [an asteraceous plant—Eds] apple orange, tomato strawberry margarine vegetable oil starch and limited amounts of gelatin whale cod and herring Vitamins and tablets containing tryptophan, valine and methionine were also given After 20 days 15 patients with rheumatoid arthritis showed subjective and objective improvement 2 with chronic discoid lupus erythema

(3) Proc. J pan Acad. 33 243 248 1957

cytoplasm. Some of the epidermal cells treated with urea showed a distinct perinuclear halo and peripheral condensation f cytoplasm. Epidermal cells of skin previously frozen or fixed were not altered by urea or lithium bromide.

These chemicals caused disruption of endothelial linings of intestine, bronchus and trachea with separation of lining cells from the underlying connective tissue and from each other Such changes were not observed in liver pancreas, and skeletal and heart muscle

Small areas of human skin exposed to 60 C. for 30 seconds in vivo resulted in erythema, edema and finally vesiculation, which usually was noticeable only microscop cally Definite acantholysis was observed in specimens removed 2-4 hours after the burn but not before. Directly beneath the acantholytic areas were inflammatory infiltrates around the superficial essels.

Work by others has suggested that tonofibrils and intercellular bridges ar closely related to keratin. The present study indicates that agents that d srupt the chemical crosslinks in keratin, the hydrogen bonds and disulfide linkages also disrupt tonofibrils and intercellular bridges. Disruption of these structures results in separation of the epidermal cells from each other a picture observed in pemphigus vulgaris benign familial pemphigus and mild in vivo burns. The keratin-lik structures of the cellular epidermis apparently are fundamental in maintaining cohesiveness of the cellular epidermal unit.

Intercellular bridges or tonofibrils have not been reported in endothelial cells, and what is responsible for their cohesion is unknown. The present study suggests that disulfide and hydrogen bond linkages play a role in the cohesiveness of endothelial cells and that all epithelium may be sim'lar in this regard.

Further Studies of Fibrous Keratin Precursor from Human Epidermis, fter extraction with 75% lithium bromide are eported by Daphne Anderson Roe[6] (Univ of Pennsylvania) Control samples were immersed in water for equal periods Significant early changes following extraction a the disruption of intercellular bridges a d tonofibrils, accompa ed by the appearance of an amorphous eosinophilic material in the upper malpighian layer and between the horny

(6) J Invest Dermat. 27:215-224 November 1956.

the aid of Knuchel's seroreaction (SR), a simple turbidity reaction, increased turbidity values were found in the serum of psoriasis patients. From these findings it may be concluded that there was an increase in the lipoprotein content (probably beta$_1$ lipoprotein) of the serum. Because increased serum lipoprotein was also found in patients with arteriosclerosis, diabetes or nephrosis and because in these diseases and also in idiopathic hyperlipemia and xanthomatoses heparin had a favorable effect with temporary reduction of serum lipids, the authors investigated whether in patients with extensive psoriasis and a positive SR the latter could be changed by intravenous or subcutaneous (depot) doses of heparin.

Sixteen patients with untreated, extensive psoriasis showing a strongly positive SR but no history of arteriosclerosis, diabetes or nephrosis were tested. In one group heparin (Liquaemin® 10,000-15,000 units) was given intravenously and the SR test was repeated after 15 and 30 minutes and 1, 2, 4 and 7 hours. Blood coagulation time was also ascertained. In the other group, depot heparin (novo lente 25,000 units) was administered subcutaneously and the test repeated after 30 minutes and 1, 4, 7 and 24 hours.

It was found that increased turbidity could be reduced by heparin doses, with even normal values occurring for a short while. When heparin was given intravenously, the effects were prompt but of short duration. After depot administration, the effects were delayed but lasted longer. The SR changes after heparin administration were different in psoriatic patients and in those with arteriosclerosis. In the latter group the turbidity cleared and disappeared earlier than in the psoriasis group, possibly because lipoprotein fractions may vary in the two conditions.

► [What happened to the psoriasis in those patients in whom the turbidity was reduced by the heparin?—Eds.]

Disruption of Epithelial Cells by Heat and Specific Chemical Agents was observed by Richard B. Stoughton[5] (Univ. of Chicago). Extensive breakdown of intercellular bridges and cytoplasmic tonofibrils occurred when fresh human epidermis was exposed for relatively short periods to urea or lithium bromide, chemicals that split hydrogen bonds and disulfide linkages. Earliest changes were observed in the disulfide linkages. Earliest changes were observed in the intercellular bridges, with later changes in tonofibrils and

(5) J. Invest. Dermat. 27:393-404, December 1956.

cytoplasm. Some of the epidermal cells treated with urea showed a distinct perinuclear halo and peripheral condensation of cytoplasm Epidermal cells of skin previously frozen or fixed were not altered by urea or lithium bromide.

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Further Studies of Fibrous Keratin Precursor from Human Epidermis, after extraction with 75% lithium bromide, are reported by Daphne Anderson Roe[8] (Univ of Pennsylvania) Control samples were immersed in water for equal periods Significant early changes following extraction are the disruption of intercellular bridges and tonofibrils accompanied by the appearance of an amorphous eosinophilic material in the upper malpighian layer and between the horny

(8) J Invest Dermat 27:119-124, November 1956.

and granular layers The horny layer was not itself affected by the extraction The amorphous material was shown to be a protein by the ninhydrin Scluff reaction it was digested by trypsin but not by pepsin (as is epidermal protein) and had an isoelectric point of about pH 4 0 (isoelectric point of epidermal protein is pH 4 5) Later in the extraction, cytolysis of the cells of the malpighian layer occurred which is interpreted to mean that in the absence of the fibrous epidermal protein the cells no longer maintain their structure

The present histologic studies seem to confirm the physical and chemical reports indicating that this protein is a keratin precursor and suggest that the eosinophilic material is identical with the presumed keratin precursor extracted with lithium bromide

Deficient Water Binding in Pathologic Horny Layers. Peter Flesch and Elizabeth C Jackson Esoda[7] (Univ of Pennsylvania) studied normal (callus) and pathologic (psoriasis, erythroderma ichthyosiforme) horny layers to determine (1) water uptake in defatted pulverized scales and their residues after extraction with water (2) free amino nitrogen determinations in nonhydrolyzed defatted scales, their aqueous extracts and water insoluble residues and (3) water extractable components that were precipitated from aqueous extracts with excess acetone and their water uptake and amino nitrogen content

Pathologic scales took up considerably less water than calluses. In all the horny layers studied the residues left after extraction with water had essentially the same water binding ability Free amino nitrogen was decreased in the pathologic specimens the decrease being restricted to the water-extractable components. The rate and extent of water binding by the precipitated water-extractable components was considerably decreased in the pathologic specimens Low water-extractable amino nitrogen with high sulfhydryl content was encountered in psoriasis only The sulfhydryl compounds in the scales can be extracted with detergents

These experiments suggest that keratinizing anomalies may result from faulty protein metabolism in the nonkeratinizing part of the epidermal cell It is not permissible to assume that an anomalous horny layer necessarily reflects an abnormal process of keratinization Present findings may

(7) J Invest. Dermat 28 5-13 January 1957

eventually help in diagnosis and therapy of scaling skin diseases. Although reduction of water-extractable amino nitrogen is not pathognomonic in itself in combination with some other characteristic chemical feature such as high SH content, it may distinguish psoriatic scales from other cornified epithelia. Studies of this nature may pave the way toward chemical diagnosis of skin diseases through chemical analyses of cutaneous constituents

The described features in pathologic scales may lead to a new approach in treatment It is clear e.g why topical therapy did not accomplish much in treatment of the 2 patients with erythroderma ichthyosiforme under study The horny layer in these patients contained little water-binding material Occlusive ointments that promote retention of water were unable to hydrate satisfactorily a horny layer that is unable to hold water in the first place.

Skin Desquamating Machine—Tool Useful in Dermatologic Research—which rapidly and conveniently carries out the Wolf Pinkus adhesive tape stripping technic, was used by Allan L. Lorincz[4] (Walter Reed Army Med. Center) in preliminary application of the method in the study of cutaneous allergic reactions barrier functions and pharmacophysiologic responses. Differences were observed in responses to histamine and trypsin applied to stripped areas, even though both produced local wheals comparable in size. Axon reflex flare was lacking about the trypsin wheal there was no intense itching and the trypsin wheal evolved more slowly and persisted longer than the histamine wheal. Preliminary application of a droplet of diphenhydramine hydrochloride inhibited whealing response to histamine but not to trypsin. It appears that the mechanism of wheal production by trypsin is not via liberation of histamine, but rather by direct action of the enzyme on the structure of small blood vessel walls to make them leaky

With use of 1 10 000 histamine phosphate periodically as the test agent, about 24 hours were required for re-formation of an effective barrier to this salt after stripping Local reactions to nickel sulfate solution in a subject with known sensitivity were more severe on a stripped site than on an area of intact skin. However reactions to 3-N-pentadecyl catechol in 3 subjects known to be sensitive to this substance

(4) J Invest. Dermat. 28 271-282, April, 1957

and granular layers. The horny layer was not itself affected by the extraction The amorphous material was shown to be a protein by the ninhydrin Schiff reaction it was digested by trypsin but not by pepsin (as is epidermal protein) and had an isoelectric point of about pH 4 0 (isoelectric point of epidermal protein is pH 4 5) Later in the extraction cytolysis of the cells of the malpighian layer occurred which is interpreted to mean that in the absence of the fibrous epidermal protein the cells no longer maintain their structure

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(7) J Invest. Dermat. 28 5 13 January 1957

ally may be metabolized via a protein pathway in epidermis because this tissue is (1) avascular and alymphatic and thus may use channels for metabolism other than those used by vascular organs and (2) continually undergoing cell division and keratinization, in which processes metabolites may be desquamated with keratin.

Propagation of Measles Virus in Strain of Human Epidermoid Cancer Cells (Hep-2) The adaptation and characteristics of the virus are reported by Francis L. Black, Magdalena Reissig and Joseph L. Melnick[1] (Yale Univ.). After human kidney passage, the virus was inoculated into a human cancer cell strain, Hep-2, which is grown in the absence of human serum and is free from cytopathogenic agents, yielding in addition large amounts of measles virus. No cytopathogenic changes characteristic of measles were seen, i.e. multinucleate giant cells with intranuclear inclusions.

Six passages were made in Hep-2 cells, but multiplication of the virus was established by showing a titer in the last harvest to be 100 times greater than that in the first. The identity of the virus was established by its characteristic cytopathic effect and by a neutralization test, using convalescent serums from patients with measles. Cultures of Hep-2 cells in Eagle medium were inoculated with the adapted measles virus and washed 2 hours later. New virus was first detectable 18 hours after inoculation when the cells were ruptured by freezing and thawing. Free virus appeared in the fluid 12 hours later with peak titers in 2½ days.

After adaptation to Hep-2 the virus was still capable of infecting monkeys, but caused little or no illness. The virus isolated from monkey's blood did not cause cytopathic changes in Hep-2 cells until after 30-56 days of incubation, suggesting that the single monkey passage had reversed partially the adaptation of the virus to Hep-2 cultures.

► [Another example of virus living in human cancer tissue. As previously noted (p. 286), tissues which have undergone malignant changes in some instances have been shown to support the growth of virus and other microorganisms without that infectious agent causing clinical evidence of disease.—Eds.]

Biologic Rhythms in Development of Healthy and Diseased Nails were studied by A. Stuhmer[2] (Univ. of Freiburg). Pitting of nails in psoriasis is a common symptom. Examination with a special binocular magnifying lens

(1) Proc. Soc. Exper. Biol. & Med. 93: 97-102, October 1956.
(2) Arch. klin. u. exper. Dermat. 204: 1-12, 1957.

were more severe on intact skin than at stripped test sites. Whealing reactions comparable to those produced by intradermal injections were observed when ragweed and orchard grass antigens were applied topically on stripped sites in a subject sensitive to these materials. No reaction occurred over intact areas. Stripped areas in a subject with severe solar urticaria failed to react with urticarial whealing on exposure to radiation which elicited intense whealing on intact skin areas.

Besides its value as a research tool the skin desquamating machine might be useful in facilitating diagnostic capillary microscopy of the skin in testing for allergic hypersensitivity and in carrying out vaccinations.

► [The difference between response of stripped and unstripped skin to certain allergens, but not to others, and to ultraviolet light deserves much further investigation. Norman Kanof and the senior editor have carried out patch tests with various allergens on stripped and unstripped skin. The results have confirmed Lorincz's findings of heightened reactivity of the stripped skin to some allergens and decreased reactivity to other. However the results are not always consistent, perhaps due to the difficulties inherent in the technic.—Eds.]

Binding of Carcinogenic Hydrocarbons to Epidermal Proteins was investigated by C. Carruthers, D. L. Woernley and J. Hittleman[9] (Roswell Park Mem'l Inst., Buffalo). The carcinogens were applied topically to the shaven back of male albino mice. Multiple applications of carcinogens were used to maintain thick hyperplasia for a good source of epidermis. It was found that the crude epidermal protein fraction of mouse epidermis bound 3,4-benzypyrene, methylcholanthrene and 9,10-dimethyl-1,2-benzanthracene in about equal amounts. Structural proteins of mouse epidermis bound more methylcholanthrene and 3,4-benzpyrene than did the crude epidermal proteins, and 3,4-benzpyrene accumulated more rapidly into these proteins than did methylcholanthrene.

Greater binding of 3,4-benzpyrene and methylcholanthrene into the structural proteins of epidermis than into the crude epidermal proteins may imply correlation between binding and carcinogenesis, but proof of this relation is not available. In fact others have shown that certain noncarcinogenic hydrocarbons are bound to about the same extent as carcinogens to epidermal proteins. There may be differences in the proteins involved in the metabolism of carcinogenic vs. noncarcinogenic hydrocarbons. Such compounds generally

(9) J. Invest. Dermat. 29: 39-45, July 195

ing point, whereas in the present study the subjects lived in a hut at 44.6-48 ? F

Slowing down of growth of the nails and hair in cold climates proves there is diminution of the metabolism of the body surface. The diminution is related to lowering of body surface temperature. Many physiologists have shown that in cold environment 2 thermal zones form in the body—a cold shell, the temperature of which can vary a great deal, and a warm core that keeps the essential organs at normal temperature. If real acclimatization to cold does exist, permanent lowering of shell temperature must be one of the chief factors. The authors interpret their measurements and those by MacLean as a test of acclimatization to the cold of Antarctica.

Cell Turnover in Epithelial Populations with reference to the slow renewal in the epidermis and the rapid renewal in the intestinal epithelium, is discussed by C. E. Stevens Hooper[4] (McGill Univ.). Cell turnover in a tissue is a process whereby cell formation is balanced by cell loss. The turnover time of the epidermal cells is that taken for the cells to be shifted from the site of formation in the deep layers to the site of desquamation on the surface. Cell turnover might be considered a repair process following trauma, but more likely is an inherent property of epithelial tissue providing a continuing supply of new cells to resist external trauma. The relative thickness of the epidermis is determined by the relation of the rate of cell production to that of cell loss. Cell production is indicated by the presence of mitotic activity in the deeper epidermis and intestinal crypts.

Various conditions and agents affect the rates of cell production and cell loss. Dietary restriction depresses both rates. Extremes of temperature alter epidermal mitotic activity which is increased as the temperature rises and decreased as it is lowered. The effect of hormones on mitotic activity of the epidermis is complex and varies with the experimental animal used. Estrogenic hormone and testosterone generally stimulate mitotic activity in the epidermis and adrenal cortical hormone and thyroxin inhibit it and lead to epidermal thinning. The effects may vary considerably depending on when the medication is administered, i.e., in which stage of the estrus cycle.

( ) J. [illegible] 131-146, November 1956.

equipped with lateral illumination (modified lens microscope of Zeiss) revealed small pits arranged mostly in transverse lines with equidistance between lesions. In one case psoriatic pits were situated atop a hardly noticeable longitudinal ridge about 1.25 mm. apart. Considering the average rate of ungual growth, this would indicate intervals of about 25-30 days between repeated pointlike psoriatic changes in the nail matrix. Similar lesions were observed on the fingers of both hands in a case described as "onychia striata et punctata periodica," but the lesions were not ascribed to psoriasis. Similar but not so regularly arranged transverse rhythmic nail changes were also seen in a patient with chronic eczema of the terminal phalanx of a finger.

In two cases of diffuse scleroderma a roof-shingle-like configuration of the nail surface showed longitudinal ridges with symmetrical formation of transverse septa. Identical nail changes were also observed in patients with psoriasis and in elderly normal persons. For this structural anomaly of the nails the term "onychodystrophia schindalamoides," meaning roof shingle, is suggested. The condition is assumed to indicate rhythmic biologic events in the growing nail with intervals of about 30 days between periods of development.

► [One of the editors, after reading this article, was surprised to find that he, too, suffers from a disease with as distinguished a name as "onychodystrophia schindalamoides!"—Eds.]

French Follow-up of Research Carried Out in 1912 by Dr. A. L. MacLean, of Australasian Antarctic Expedition, 1911-1914, on Slowing Down of Growth of Hair and Nails in Antarctica. J. Sapin-Jaloustre (Paris) and T. H. Goddard[1] (Hobart, Australia) measured nail growth by adjusting a small piece of metal to a permanent mark on the nail, then recording the movement of the metallic piece in relation to the bone of the finger by x-ray. Hair growth was studied by shaving an area, then shaving it again 2 months later. Average length of many hairs was considered as the amount of growth during this period. Growth of nails and hair in Antarctica was about 0.6 that recorded for a temperate climate (France). In 1912, MacLean found about the same rate of growth of nails in Antarctica, but rate of hair growth was only about 50% of the present figure. This might be explained by the more severe conditions under which the subjects lived in the first study. Their hut had a temperature near the freez

(1) M.J. Australia 2:639-641, Oct. 27, 1956.

mg point, whereas in the present study the subjects lived in hut at 41.6-48.2 F

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(4) J Kmedum, 53 348, November 1954

Turnover time of intestinal epithelium is from 1½ days to 1 week compared to the epidermis which is 13-100 days. The presence of food in the gut may play an indirect role in cell turnover by increasing villus activity either directly or through nervous reflexes with consequent cell extrusion. In the intestine cell extrusion has been shown to proceed independently of change in the rate of cell formation Hormones influence cell turnover in the intestinal epithelium with reduction in mitotic activity having been noted in the intestinal crypts after thyroidectomy and hypophysectomy in rats. The appearance of the intestinal epithelium is remarkably constant considering its rapid rate of renewal and the delicate balance between cell production and loss

In contrast with nonrenewing tissues whose architecture is always constant the histologic picture of an epithelium undergoing renewal may vary with the interplay of factors controlling its cell turnover

Quantitative and Qualitative Data on Pigment Cells of Adult Human Epidermis Renato J Staricco and Hermann Pinkus[5] (Wayne Univ) identified melanocytes by the dopa reaction and counted them in separated epidermal sheets of 63 surgical specimens of normal white and Negro skin from 7 major regions of the body A mean of 1 155 cells/sq mm was determined but individual counts ranged from 400 to 2,784 and mean values for various regions from 754 on the abdomen to 1 668 on the male genitals Very dark epidermis did not contain more melanocytes than light skin.

Melanocytes of Negroes seem to be generally larger and more dendritic than those of light skin There appears to be a parallelism between length and number of dendrites and melanogenic activity Support for this hypothesis is found in the greater size of melanocytes after moderate stimulation by thorium X and in the gradual increase of size of fetal melanoblasts

Melanocytes which are dendritic cell are always distinctly different from malpighian cells. No intermediate forms were observed Melanin granules are found also in the malpighian cells of normal and various types of pathologic skin and can be identified in all layers of the epidermis Under certain pathologic conditions (certain senile keratoses lichen planus and certain cases of dermatitis) melanin may

(5) J Invest. Dermat. 28 33-45, January 1957

be found in large quantity in melanocytes, but little or none is contained in the malpighian cells. Under these conditions, a pathologic block seems to exist, which does not permit the melanocyte to discharge its granules or prevents the malpighian cell from accepting them.

Human Melanocytes in Tissue Culture Funan Hu, Renato J Staricco, Hermann Pinkus and Robert P Fosnaugh (Detroit) studied melanocytes of benign pigmented nevi and of foreskin of white and Negro infants grown in vitro by the roller tube technic. Dendritic cells giving positive dopa reactions, containing argentaffin pigment granules and presenting other characteristic morphologic features, were observed in many cultures and identified as melanocytes. The cells appear to represent a distinct type. During several weeks f observation of the two types seen in the epidermis (epithelial cells and melanocytes) no transformation of one cell type into the other was observed Each cell apparently gives rise to daughter cells of its own specific type

There was no apparent difference in the number of melanocytes found in cultures of white or Negro skins. The main difference was the amount of melanin granules the cells contained. The melanocytes of Negro skin seemed to have more processes and branches but the difference was not great

Melanin granules were present not only in the dendritic cells, but also in some epithelial cells and fibrocytes. Some or all of the pigment in the outgrowing ep dermal cells may ha e been carried along from the original explant. The presence of melanin in fibrocytes must be attributed to phagocytosis. Sometimes there was difficulty in differentiating melanocytes from young fibrocytes (Fig 61) in cultures stai ed with May-Grünwald-G emsa reagent. The epithelial and fibrocytic portions of the outgrowth were not stained by the dopa technic, thus indicating the specificity of the reaction.

Two types of melanocytes were observed in nevi—the mall type as ordinarily seen in normal epidermal outgrowth and a large ariety The latter were 2-4 t mes larger than the small type, reacted strongly to dopa reagent and became filled with black granules. The opinion that nevi are simply an excess accumulation of normal melanocytes does not explain the wide differences in sizes of these cells. The activity of pigment synthesis seemed to be correlated with the size of

(6) J Invest Dermat 28 1 22, January 1957

pigment cells. If this thesis proves true the increase in number and size of melanocytes in nevi may be merely an expression of increased functional activity of these cells as a result of some unknown stimulation. It is also possible that nevus cells may represent the transformation of normal pigment cells into a variety of tumor cells similar to the change of epidermal cells into benign epitheliomas. In the present cultures the dermal element of nevi was not capable of active proliferation. This finding seems to confirm the view



Fig. 61.—Bipolar melanocytes with one process extending close to nucleus of epithelial cell. Note collection of pigment granules in form of nuclear capping adjacent to process of pigment forming cell. M. Grünwald Giemsa stain, reduced from × 970. (Courtesy of Hu, F. et al.: J. Invest. Dermat. 28:15-32, January 1957.)

that intradermal nevi are composed of relatively quiescent, inactive melanocytes which gather in the corium after dropping down from the epidermodermal junction.

► [Although there are distinct drawbacks and shortcomings to the in vitro method of cell growth on culture mediums, this method has made possible numerous informative investigative studies in dermatology. There will come a point, however, where in vivo technic will again have to be resorted to.—Eds.]

Mucocutaneous End Organ: Primary Organized Sensory Ending in Human Skin. R. K. Winkelmann[7] (Mayo Clinic) recently studied neural tissue in man using a technic involving impregnation of frozen sections with silver. Histologic examination of the mucocutaneous zones between haired skin

(7) A.M.A. Arch. Dermat. 76:225-235, August, 1957.

and true mucous membranes disclosed the presence of a distinct sensory end organ termed the mucocutaneous end organ. The end organ is composed of loops of nonmyelinated nerve fibers rolled on one another into a spherical or oval mass (Fig 62) The individual fibers maintain their integ rity giving off branches but not anastomosing with other fibers. From 2-6 myelinated fibers enter the end organ. These organs were found in the glans penis, clitoris, prepuce,



Fig 62—Typical mucocutaneous end organ as seen from below in horizontal section of adult prepuce (section stained with silver); reduced from × 470 (Courtesy of Winkelmann, R K A M A Arch Dermat 76 225 238 August, 1957)

hermaphroditic genital organs, the perianal region, lip tongue and eyelid They were not found in haired skin, true mucous membranes or the distal regions of glabrous skin. The fully formed end organs were not found in the prepuce of newborn humans, although th y were numerous and char acteristic in adult tissue. The endings were found chiefly in the *bpapillary layers of the dermis*, but in the prepuce, eyelid and lip they were also found in the papillae.

The mucocutaneous end organ appears to be found only in primates, as the *end organ in cats is a different end bulb* structure. In view of its l mited locatio the mucocutaneous

end organ cannot have an exclusive general function. It is *suggested* that in common with the hair follicle innervation from which it may be derived, it has the ability to allow perception of touch. The morphologic characteristics and location of this end organ in the skin could account for the acuteness of this perception.

As a result of his study of representative tissue from all types of human skin, the author believes that various distinct neural forms exist. The networks of nerves and the hair follicle endings constitute the major portion of the cutaneous neural tissue. The hederiform endings of Merkel Ranvier and the Meissner corpuscles are present in the distal glabrous skin of the hands and feet. In the mucocutaneous regions of the body is found the mucocutaneous end organ. The Vater Pacini body may be found in any glabrous type of skin. The papillary nerve is present in all types of skin and is derived from the networks of nerves; however, it is well developed only in glabrous regions.

Neurohistology and Neurophysiology of Itch Sensation in Man were studied by Walter B. Shelley and Robert P. Arthur[8] (Univ. of Pennsylvania). For demonstration of punctate sensibility to a chemical stimulus, single cowhage spicules were used. They contain an active pruritogenic proteinase, mucunain. Only when a spicule was inserted into an itch point was the sensation of pruritus experienced. Between itch points are inert areas that do not respond to chemical stimuli. Insertion of a spicule to a depth of 50-100 µ is enough to initiate itching. Pruritus is not produced by insertion of spicules into capillary loops or eccrine sweat pores. Variable results are obtained in hair follicles.

Ten sympathectomized patients had normal itch points and itch thresholds. In areas of sensory denervation, however, cowhage spicules were without effect. Spicules produced a small area of inhibition about them so that subsequent spicules were without effect if placed with 100 µ. Under electric testing, areas of this size showed 4 or 5 itch points. Spicules of cowhage in the cantharidin vesicle base elicited definite pruritus, indicating that the epidermis is not critical in producing proteinase pruritus.

Itch points responded to many other punctiform stimuli. The simplest stimulus was a fine springy tungsten wire. In

(8) A.M.A. Arch. Dermat. 7: 296-323, September 1957.

activated cowhage spicules were soaked in 1% trypsin solution, dried and inserted in itch points. They produced an intolerable degree of itching lasting as long as 30 minutes. Similar results were obtained with histamine. The alternating current square wa e stimulator produced itching in absence of clinical signs. *Direct current stimuli from the stimulators and use of the Bov e electrolysis unit at its lowest* setting also produced pruritus but these technics were under poorer control and tended to produce gross tissue damage.

The authors were able to modify the classic methylene blue nerve stain to permit consistent, uniform staining in vivo of all neural elements in human skin. Physiologic and histologic findings were correlated by studying large superficial shavings of skin in which active or inactive cowhage sp cules remained as markers. By this method the itch point was shown histologically to be a rich aggregate of fine fibers in the subepidermal area. Itch points in which the spicule gave *the longest*, most intense itch had the greatest supply of fine nerves and endings. S tes in which the itch came late and persisted only a minute or two had relatively sparse nerve supply The silent areas were devoid of fine fibers or showed only a few On occasion negative spicules were found near large nerve bundles indicating that proteinase does not a tivate nerve trunks directly Intraepidermal nerve elements were *not noted. No encapsulated or organized nerve units* were found at itch sites Study of ertical sectio s indicated that itch points epresent a complex intermixture of A and C fibers

Pruritus can be elicited regularly in man by intradermal introduction of various endopeptidases The purest, most effective preparation available for testing is crystallized lyophilized trypsin. *Injection must be very superficial.* The amount must be small (0 05 cc or less) as large amounts in ariably failed to produce itch A fresh acti e product must be used in proper concentration. For lyophilized tryps n the threshold concentration for producing pruritus is near 1/100,000. Concentrated solutions (1/100) may produce a purpuric vesicle or bulla Injection of heparin (1/1,000) n tradermally inh bits the *pruritogenic action of trypsin but* because of its specificity t has no effect *on cowhage. With di*lute proteinase or with superficial insertion of single cow

hage spicules little or no clinical change in the skin is observed

Evidence that itching is mediated by the fine unmyelinated C fibers rests basically on three points Histologically itch points have been shown to be composed of many fine nerve endings for small and large cutaneous afferent fibers. Proteinase the adequate stimulus for pruritus fails to elicit the sensory modalities associated with large or A fibers (touch and prick pain) whereas it may elicit burning pain long associated with the fine C fiber function. Pruritus cannot be perceived instantly when initiated on the extremities by mechanical or electric stimuli There always is a latent or lag period compatible with neuron conduction rates of 2 m./second, *as required for fine or C fiber transmission. Great differences* were noted in itch sensitivity in different persons and in different areas of the body One of the most prominent considerations in explaining this difference in response appears to *be the density of fine fiber innervation*

Since mechanical stimuli produce pruritic sensation lasting only a few seconds whereas chemical stimuli produce response that lasts for minutes it is probable that chemostimulation is responsible for the common clinical situation. The most promising therapeutic approach seems to be an attack on the fine naked nerve endings Possibly intravenous anesthetics and calcium act in this way Local cooling of skin temperature must exert its effect in this fashion at least in part Although it has been shown that local injection of proteinase inhibitors prevents proteinase pruritus this approach is not practical from the clinical standpoint Many different kinds of proteinase may be acting on the nerve ending but no broad spectrum antiproteinase is known Furthermore disturbance of the proteinase economy in the body especially the blood-clotting system could be extremely dangerous

► [This excellent article shows how far our knowledge of *itching* has progressed since Hafenraffer defined it 200 years ago as "that disagreeable sensation which excites the desire to scratch. —Eds]

Chemical Causes of Pain and Itch are discussed by C A Keele[9] It was formerly thought that free unencapsulated nerve endings were concerned only with pain *but recent* work has shown that all forms of cutaneous sensation can be felt in skin that does not possess specialized encapsulated

(9) Proc Roy Soc Med. 50 477-484 July 1957

endings. This indicates that some of the free nerve endings must be involved in perception of temperature and touch as well as pain. Work on chemical production of pain by the author and that of others on itch can be readily linked with distribution of free nerve endings in epidermis and different levels in the dermis. It appears that intraepidermal nerve endings are concerned only with itch and the dermal endings with pain.

Receptors for itch therefore must be situated on the axoplasmic filaments running between, but not into the cells of the epidermis penetrating as far as the stratum granulosum. These receptors can be stimulated by histamine and proteolytic enzymes but not by other substances such as potassium or 5-hydroxytryptamine (5-HT) They also can be activated by mechanical, thermal and electric stimuli at intensities below those causing pain. When the epidermis is removed, itching can no longer be elicited because the appropriate receptors are gone Since occurrence of itching is related to the so-called pain spots in the skin and since nerve fibers conveying itch run up the anterolateral tracts of the spinal cord it is assumed that the itch fibers though independent of pain fibers, pursue the same anatomic pathway The only differences are at the very periphery and presumably also in the central nervous system where the pathways end.

With these assumptions, it is easy to explain how itch can be felt at all intensities without any element of pain. It also is possible to explain how pain can be felt even at the lowest intensity without any trace of itch, and how both sensations can be felt simultaneously

Evidence is presented that the quality of pain may differ even at different levels in the dermis. On the blister base the typical immediate smarting pain produced by acetylcholine differs in character from the delayed duller pain of 5-HT or plasma pain-producing substance. Difference in time of onset suggests that acetylcholine acts on nerve endings right on the surface of the exposed base and that 5-HT and plasma pain-producing substance act on deeper nerve endings.

Keele did not study subcutaneous or deeper pain receptors, but they probably also show selective sensitivity to chemical and physical stimuli and the pain produced is certainly different in quality from that evoked in superficial structures.

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(9) Proc Roy Soc. Med 50 477 484 July 1957

ease. Such a mechanism might apply not only to the skin but also to a variety of surface, subsurface and deep disease processes.

Control Study in Psychosomatic Dermatoses Psychiatric Survey of Patients with Pityriasis Rosea. One of the difficulties in evaluating the role of emotional factors in skin disease has been the relative lack of satisfactory control studies. Samuel I. Greenberg[2] (State Univ of New York, New York City) selected 30 patients with pityriasis rosea for psychiatric examination as a control study because the seasonal occurrence, self-limited course and rarity of recurrence of this disease make it extremely unlikely that it can be a psychosomatic condition Of the 30 patients, 19 were psychoneurotic and 3 were borderline psychotics. Thus about 73% were mentally disabled. Four of the patients gave a history of severe emotional trauma preceding onset of the eruption. The suggestion that the condition was emotional in origin was readily accepted by 21 (70%) of the patients

Results suggest that caution must be exercised in assuming that coexisting mental illness or preceding emotional trauma are of causati e relation in dermatoses of as yet undetermined cause.

► [W agree with the author who is fully trained dermatologist and psychiatrist, that control studies such as this are indeed necessary in order to evaluate the role of emotional factors in skin diseases. Greenberg work cannot help but cast doubt on many previous reports which claim psychosomatic and emotional causes for certain dermatoses.

T evaluate the psyche as cause or important contributory factor of somatic disease, it is necessary to include not only proper controls but also to have sufficiently definite criteria to establish or rule out psychiatric disease. The vagueness of the limits of normality and abnormality make it extremely difficult to carry out studies on psychosomatic relations that will stand up under close scrutiny.—Eds.]

Relationship between Acne and Hair Growth. R. N R. Grant[3] (Workington, England) confirmed an earlier observation that hairs do not issue from follicles containing comedones. When comedones were expressed, it was noted that often what appeared to be sebum was left protruding in a fine tail from the follicle. Closer inspection revealed that this was a fine hair covered with sebum. The comedones that had been removed were cleared in liquid paraffin or immersion oil and were found to contain one or more hairs.

Examination of the lanugo hair on any part of the body

(2) A.M.A. Arch Dermat. 76 24-26, July 1957
(3) Ibid., pp 179-184, August, 1957

Studies on Pain Relation between Cutaneous Vasodilatation Pain Threshold and Spontaneous Itching and Pain was investigated by David T Graham Helen Goodell and Harold G Wolff[1] (New York Hosp -Cornell Med. Center) Thresholds for pain of pricking quality on the skin of the back during control periods were compared with those obtained during cutaneous vasodilatation induced by immersion of the legs in hot water i e., reflex effects and by administration of nicotinic acid Mecholyl® and Priscoline® Thermal and mechanical methods of estimating pain sensitivity were used.

The pain threshold was lowered during the initial phases of vasodilatation at which times the subjects reported increased itchiness This effect was not mediated solely by temperature rise accompanying vasodilatation because the critical level of skin temperature at pain threshold was lowered and because heating the skin with hot air to the temperature occurring with vasodilatation did not lower the pain threshold. Lowest pain thresholds during induced vasodilatation usually were obtained as the skin temperature was rising and sometimes they returned toward control levels during the period of maximal elevation of skin temperatures. This indicates that lowered pain threshold of the skin was intimately associated with initiation of vasodilatation rather than the fully vasodilated state.

It is suggested that these observations explain the association of flushing of the skin and itching in patients with a host of skin disorders Since noxious stimulation barely at pain threshold intensity induces itching it is reasonable to suppose that many mild stimuli ordinarily nonnoxious and not perceived, give rise to itching in which the pain threshold is lowered in association with vasodilatation

The authors hypothesize that during the initial phase of vasodilatation there is liberated locally into the tissues an agent (or agents) that injures tissue and lowers the pain threshold When the amount liberated is minute as during onset of reflex vasodilatation the pain threshold lowering effect is slight and transient and short lived itching may be one effect When the amount of agent liberated is greater and persists longer as with inflammation after skin injury with heat the vasodilatation and pain threshold lowering effect is also prolonged and spontaneous pain or itching may

(1) Am. J M. Sc. 234:420 430 October 1957

impressive, but the role of feeble pilomotor muscles should be investigated further

On the basis of the study Cohen suggests that comedones apparently form in pilosebaceous follicles in which the hair is rudimentary Seborrhea is present and hormonal influences cause follicular hyperkeratosis. The pilosebaceous follicle being one physiologic entity the more sebum produced, the smaller the amount of keratin (hair) formed. Follicles with lanugo hairs usually have small pilomotor muscles

Thus, excess sebum is formed and meets a narrowed hyperkeratotic follicular ostium. The small hair cannot push its way through the ostium and act as a drain for the sebum. At the same time, the pilomotor muscles are too small and weak to help propel the sebum to the surface. If the sebum is abnormal physically or chemically this may also contribute to comedo formation.

▶ [The lesion of acne vulgaris is an excellent illustration of the astounding number of factors which contribute to a single type of lesion. What is the role of hyperkeratosis at the follicular opening and in the duct of the sebaceous gland, of hyperactivity of a normal-sized sebaceous gland, of hyperactivity of an enlarged sebaceous gland, of the rudimentary hair of temperature, of humidity, of external manipulation, of foods, of drugs, etc.? And what is the mechanism by which foods, such as chocolate, and drugs, such as bromides, exert their aggravating effects in acne? These and many other questions regarding acne vulgaris still remain to be answered —Eds]

Keratinization of Duct of Sebaceous Gland and Growth Cycle of Hair Follicle in Histogenesis of Acne in Human Skin. Pilosebaceous structures in normal human skin and acne were studied by Eugene J Van Scott and Ross C. MacCardle[5] (Nat'l Inst of Health) from horizontally cut serial sections and reconstructed balsa wood models enlarged 75 times. No follicular unit of the beard or scalp had more than 1 hair shaft whereas about 50% of the follicular units of the skin of the back had 2 distinct hair roots originating from the lower portion of a common follicular neck. The follicular neck of pilosebaceous units in skin of the beard contained 2 distinct channels the hair shaft traversed one, whereas the other connected the excretory duct of the sebaceous gland directly with the surface pore.

Earliest change of acne was hyperkeratinization of the excretory duct of the sebaceous gland, which results in deposition of a keratinous plug in the follicular neck. The keratinous plug was continuous into the mouth of the sebaceous

(5) J Invest. Dermat. 27:405-429 December 1956.

with a lens revealed that in a proportion of follicles containing a mature hair part of the succeeding hair was penetrating the orifice at the base of the mature hair Grant hypothesizes that absence of an effective hair from the follicular orifices may precipitate comedo formation Thus in a follicle subject to androgenic stimulation at puberty in such a way as to produce hyperkeratosis and seborrhea temporary absence of an effective hair penetrating the mouth of the follicle will make the discharge of sebum and cellular debris so difficult that a comedo forms If this hypothesis is correct it should be possible to show a relation between the degree of acne in a patient and the proportion of follicles in the affected area that show succeeding hairs "

The relation of the proportion of visible succeeding hairs to the degree of acne as measured by the number of comedones present was investigated Many patients were examined, and 50 follicles in each were carefully inspected The number of follicles that showed succeeding hairs was found to decrease with increased severity of the acne. The findings confirm the expected relation between severity of acne and rate of replacement of the lanugo hair Variations of succeeding hair index and clinical state were recorded in patients who attended with comparative regularity and variation of this index in individual patients paralleled the clinical state with remarkable accuracy

Mechanism of Comedo Formation in Acne Vulgaris. E. Lipman Cohen[4] (St Bartholomew s Hosp London) reviews the various hypotheses of the mechanism of comedo formation as found in the literature Some theories depend primarily on the relation between hyperkeratosis altered sebaceous secretion and infection whereas others connect primary weakness in hair growth with feebleness of the arrectores pilorum muscles

In seborrheic states and therefore in acne vulgaris the earliest change probably involves hyperkeratosis but the presence of hyperkeratosis is no proof that it is a major factor in acnegenesis " Whether the sebum is altered in acne is still unknown Bacteria play a part in producing the secondary lesions in acne though it is not certain that they are primary factors in the formation of blackheads Evidence that weakness of the hair in the follicle is an important factor is

(4) Brit. J Dermat. 68 362 368, November 1956.

of the sebaceous gland. The products of the sebaceous gland may biochemically initiate the hyperkeratosis.

A large percentage of hairs involved in the early lesion of acne of the back were found to be in the resting (telogen) phase of the growth cycle. This may suggest that a growing hair maintains its follicular lumen free from keratinous ma-



Fig. 64.—Late stage lesion of acne in pilosebaceous unit of beard of man, 34. Kera[illegible] of lumen attached to left side of unit with large mass of pus, showing small [illegible] material which represents contents of sebaceous duct. Height of actual model, 1 in. (Courtesy of Van Scott, E. J. and MacCardle, R. C.: J. Invest. Dermat. 27:405-429, December 1956.)

terial thus preventing formation of the keratinous plug of acne. However, hyperkeratosis of the pilosebaceous structure of the beard was found to be confined to the sebaceous channel. Since this channel is isolated from that which the hair traverses, state of growth of the hair should have no physical influence on keeping the sebaceous channel clear of debris. This suggests that cyclical qualitative or quantitative changes in the sebum may be correlated with the hair growth cycle to bring about hyperkeratinization of the excretory

gland (Fig 63) The orifice of the gland was dilated and filled with keratinous substance In a pilosebaceous unit of the beard in a later stage of involvement with acne, pus was found only in the sebaceous channel (Fig 64) In the late stage of acne of the back the lumen of the entire follicular neck was completely occluded with a keratinous plug that was anatomically associated with the hyperkeratotic excretory duct of the sebaceous gland Pus was present at the



Fig. 63—Lesion of acne. Pilosebaceous unit of upper back of girl, 18. Horizontal section at level of orifice of duct of sebaceous gland (at right) Note dense (black) keratinous material that occludes follicular lumen and sebaceous duct. Gomori trichrome reduced from × 400 (Courtesy of Van Scott E J and MacCardle, R C. J Invest. Dermat 27 405 429 December 1956)

lower most level of the follicular neck apparently compressing the keratinous material above it into a more densely packed plug that completely occluded the surface pore

Since the earliest recognizable histologic alteration in development of a lesion of acne is hyperkeratinization of the excretory duct of the sebaceous gland it appears that the excretory duct of the gland is the primary focus of the acne lesion This conclusion is supported by the finding of hyperkeratosis of the pilosebaceous units of the beard confined solely to the compartmentalized channel within the follicular lumen that was in direct continuity with the excretory duct

especially after the keratin plug has formed. Eventually the epithelial follicular wall is disrupted by the primary toxic ef fect of the chemical enabling the foll cular contents to escape into the corium, where again by primary toxic effect a violent inflammation is provoked. Chloracne thus appears to be a chemical dermatosis. Some additional property of Halowax is necessary to explain the development of comedones, for there are many types of chemical irritants which evidently lack this capacity Irritation of the follicular wall, however is doubtlessly a contributing factor in hyperkeratosis.

Constitutional Factors in Acne Vulgaris Prevalence in White Soldiers and Lack of Association with Ancestry Complexion, Body Hair Blood Group, Handedness, Plasma Pepsinogen and Physique, including height, weight, the height weight ratio, weight in relation to age height standards somatotype and gynandromorphy (morphologic masculin ity) is reported by Albert Damon (Columbia Univ) The subjects were 400 consecutive white soldiers aged 17-29 Most fell between 18 and 24 with a mode of 19 and a mean of 21 years Some degree of clinical acne was present in 40% of the group. The findings differ from those of two ecent Brit ish reports suggesting that physique may play a part in the etiology of acne.

Relationship between Skin Hydration and Suppression of Sweating was studied by Walter C. Randall and Clarence N Peiss[8] (Loyola Uni) Sweating responses were ecorded by the iodine-starch paper method before and after immer sion of the hand or finger in various aqueous solutions. It was found that coincident w th the wrinkled and wh tened appearance of the palmar skin immersed in water sweating is suppressed. The suppression is most intense when the im mersion water s warm (25-40 C.) and does not occur or is mu h less intense when the water is cold (5-15 C.) Immer sion of the hand in saline solution results in suppression of sweating in inverse proportion to the NaCl concentration. Suppression in 1% saline solution is comparable to that induced by water Immersion in 3% saline solution results in less complete suppression. In some subjects, 7% saline solution produced moderate to marked suppres ion while in others it did not. In very few subjects did 10% solutions pro-

(7) A.M.A. Arch. Dermat. 76 172-178, August, 1957
(8) J. Invest. Dermat. 28 435-441, June, 1957

tract, thus initiating formation of a keratinous plug in the follicular neck.

► [The original of this article should be read, in particular for the series of plates showing models of pilosebaceous units of human skin. The findings and conclusions are indeed provocative and contribute to our knowledge of the pathogenesis of acne vulgaris.—Eds.]

Experimental Production of Acne by Penta- and Hexachloronaphthalenes applied to the back, face, leg, axilla, scalp scrotum and ear (pinna) of 31 white and Negro men is reported by Walter B Shelley and Albert M Kligman[6] (Univ of Pennsylvania) Daily application of a mixture of penta and hexachloronaphthalenes (Halowax 1014) as a 50% suspension in mineral oil invariably resulted in production of comedones within 4-6 weeks Except on the scalp and scrotum inflammatory lesions subsequently developed over a 6-month period although naphthalene applications were stopped at the end of 2 months In the axilla the inflammatory acne which developed presented the characteristic clinical picture of hidradenitis suppurativa with nodules sinuses and abscesses On the back an alarming fulminant inflammatory acne indistinguishable from acne conglobata developed in every subject The disease remained in an active angry state for several months and then slowly resolved over the next half year Residual scarring hyperpigmentation and other characteristic sequelae of acne conglobata remained

The histologic basis for the comedo follicular hyperkeratinization could be observed within 1 3 weeks. Sebaceous glands disappeared or became much smaller The first prominent change leading to inflammatory acne was perifollicular aggregation of polymorphonuclear leukocytes. This was followed by intrafollicular collections of leukocytes. The cardinal event was destruction of the follicular wall with outpouring of follicular contents into the dermis leading to abscess formation The inflammatory sequence unfolded exclusively in follicles containing well-developed comedones A quite different situation prevails in acne vulgaris inflammatory lesions usually do not develop from clinically prominent comedones

In chloracne, the abscess contains a large keratinous "seed rarely present in natural acne. Apparently the Halowax, a known irritant and toxic agent piles up in the follicle,

(6) A.M.A. Arch. Dermat. 75 689-695 May 1957

of the donor site and elsewhere but was absent in the transplant and palmar skin

These observations indicate that, although skin transplants retain the locally determined characteristics of the donor site structures in the skin under neural control develop the physiologic responses of the new area.

[These findings are in consonance with what one would have expected, i.e., that the skin grafted onto the finger would develop the physiologic responses of the receptor area including the neural control which accounts for emotional sweating of the hands. However, to clinch the point it would be necessary to show that skin from the finger grafted onto the abdomen or forearm also takes on the sweat characteristics of the receptor area.—Eds.]

Succinic Dehydrogenase Activity of Eccrine Sweat Glands in Facial Hemihyperhidrosis is reported by Kimmo K. Mustakallio[1] (Univ. of Helsinki).

Man, 27, had had continuous sweating of the right side of the face and scalp for 4 months; the left side was normal. Hyperhidrotic areas were delineated by Minor's iodine-starch test. Laboratory findings and physical examination were essentially normal. An intravenous dose of tetraethyl ammonium chloride, 7 mg./kg. body weight, prevented sweating for only 10 minutes. 2 mg. atropine sulfate subcutaneously was required to suppress perspiration for 4 hours. Punch biopsy specimens were taken from symmetrical temporal sites, incubated, treated with neotetrazolium, fixed and mounted. Cells of the hyperhidrotic eccrine sweat glands from the right side of the face showed more dense deposits of purple diformazan crystals than the cells of the normally perspiring glands from the left side. The duct cells in the secretory coil were most heavily laden with the crystals. Staining with hematoxylin-eosin revealed no noticeable difference between the two sides.

More intense succinic dehydrogenase activity occurred in the hyperhidrotic sweat glands, especially their ducts, than in the normally perspiring glands, probably indicating an adaptation to the higher energy requirements by the overactive cells.

Measurement of Electric Conductivity of Sweat: Its Application to Study of Cystic Fibrosis of Pancreas. There are a limited number of pathologic states, such as adrenal dysfunction and cystic fibrosis of the pancreas, in which significant alterations of sweat composition have been noted. In cystic fibrosis of the pancreas the alterations are of such magnitude that measurement of the electrolyte content of induced sweat is a reliable diagnostic procedure.

Truman S. Licht, Milton Stern and Harry Shwachman[2]

(1) Acta dermat.-venereol. 34:278-282, 1954.
(2) Clin. Chem. 3:37-48, February, 1957.

duce suppression while 20% NaCl frequently accentuated sweating

The architectural arrangement of keratin around the poral orifice of the sweat duct together with its hydrophilic properties suggests that the degree of sweat suppression is related to the uptake of water by keratin This results in swelling of the keratin ring and mechanical occlusion of the sweat duct When the skin is re-exposed to an environment with a relatively lower vapor pressure, the water of hydration is lost with a gradual recovery of sweating

There is some similarity between the phenomenon of sweat suppression during immersion with that occurring in the sweat retention syndrome In many instances, the decisive factor in retention is formation of a keratin plug at the poral orifice Perhaps prolonged hydration as induced by immersion would produce similar architectural changes but thus far the relatively short periods of immersion have produced only temporary sweat suppression

Acquired Emotional Sweating in Transplants. Eccrine sweat gland function of the palms and soles in man is distinctive Volar sweat glands respond characteristically to emotional mental or sensory stimuli whereas those of the general body surface are activated primarily by heat. These functional variations of the eccrine sweat gland have been attributed to the differences in the site of origin of the nervous impulses initiating such responses, and not to any anatomic alteration of the glands themselves or in the nerves supplying them. Eccrine sweat glands from all areas show an identical cholinergic innervation Thermal sweating has been ascribed to impulses originating in the hypothalamus, while the impulses for emotional eccrine sweating are believed to emanate from the cerebral cortex.

Additional support for this hypothesis may be derived from observations made by Harry J Hurley Jr and Walter B Shelley[9] (Univ of Pennsylvania) In 2 subjects full thickness skin grafts from the general body surface transplanted to the volar surface of the hand displayed emotional eccrine sweating as did the rest of the palmar skin whereas no emotional sweating was evident in and adjacent to the donor sites (abdomen forearm) In 1 subject who was also studied after heat thermal sweating occurred in the region

(9) A.M.A. Arch Dermat. 75 815 818 June, 1957

indicator oil The paper was then applied to the skin and covered with a short glass rod of the same diameter and a pressure of 50 Gm. was applied on the rod for 10 minutes The paper was removed moistened with 0.005 ml. toluene or ether and transferred on the oil. Recovery by this method was high and reproducibility excellent with the coefficient of variation 4-15%

Some Observations Concerning Enzymatic Activity and Lipid Film on Human Skin. Franz Herrmann Leonard C. Harber Richard Scher and Leona Mandol (New York Univ Post-Grad. Med. School and Skin and Cancer Unit) assayed lipid samples from 21 different areas of the skin surface of different subjects to ascertain (1) the lipid quantity by weighing (2) the spreading index of the lipids (the square centimeter area of water surface covered by 1 µg lipid in a sample) and (3) the acid number of the lipids.

The spreading index was paralleled by the acid number as lipids from a given skin area in subjects with a high spreading index for this area generally showed also a high acid number whereas the acid number was low in lipids collected from the analogous area in subjects with a low spreading index for this site Similarly in the same subject, a higher acid number was as a rule obtained in samples from skin areas with a high spreading index than in samples from the area with a low index.

During the warmer season, the spreading index distinctly tended to increase In general, this increase was higher for skin areas which yielded a low index and tended to dry out during the cool period than for skin areas which also during this period yielded a high index and tended to show moisture. The differences obtained for different skin areas and seasonal variations appear to be largely due to differences in liberation of free fatty acids from their esters by esterase activity The indications are that the different degrees of enzymatic activity to a great extent depend on distribution of the microbial flora on the skin. It seems pertinent that the rise in the quantity of free fatty acids was slight or reversed in areas which tend to be moist from sweating (mid upper chest, soles) and for this reason always tend to harbor many microbes The pronounced rise, on the other hand, occurred on sites where dryness prevails in a cool atmosphere but where

( ) A.M.A. Arch Dermat 76 282-287 September 1957

(Boston) describe a method for measurement of the electric conductivity of thermally induced sweat A mean value of 16 150 micromhos/cm was found in 47 children with cystic fibrosis of the pancreas In 77 children, of which 6 were healthy and the others had miscellaneous illnesses the mean value for the sweat conductivity was 5 560 micromhos/cm. All the subjects with sweat conductivities less than 9,000 micromhos/cm did not have cystic fibrosis all with sweat conductivities greater than 12,000 micromhos/cm with one exception had cystic fibrosis The intermediate range (9 000-12 000 micromhos/cm) comprised less than 10% of the subjects studied.

Evaluation of these data and studies now in progress indicate that the measurement of the concentration of chloride and/or sodium in sweat is a more reliable diagnostic index of cystic fibrosis of the pancreas than is the sweat conductance measurement

Methods for Determination of Oiliness of Skin were critically evaluated by K Fiser and S Fiker[3] (Prague) The experiments dealt primarily with sampling methods of the skin secretion and with transfer of the samples These procedures were found to be responsible for poor reproducibility and great scatter of the data. For quantitative determination of the lipid substances a method originally developed by Jones has been adopted as most sensitive The principle of this method is that lipids form a defect on the polymolecular layer of an indicator oil The size of this defect is easily measurable and proportional to the content of lipid substances

Adsorption of the skin secretion on a polished glass rod used most frequently as a sampling procedure was tested on models with known concentrations of oleic acid stearic acid cholesterol and skin extracts When the sample was transferred directly from the rod to the indicator oil the recovery was only 4-42% and the coefficient of variation was 6-130% Better results were obtained if the exposed part of the glass rod was moistened with 0 004 ml ether and the sample transferred immediately after the ether had evaporated. In another series of experiments round pieces of filter paper 5 mm in diameter were used instead of glass rods The pieces were first extracted with ether for an average of 6 hours until no defect formed when they were placed on the

(3) Ceskoslov derm 31 315 320 1956

Histology of Reactions to Light. G Miescher[4] (Univ of Zurich) investigated the histologic reaction to different radiations. These reactions were different from the character istic short wave ultraviolet light reactions. The following reactions were studied (1) those due to long wave ultra violet light, (2) those elicited by visible and infra red rays, (3) those due to photodynamic catalysts and (4) photoallergic reactions.

The classic reaction to short wave ultraviolet rays is characterized by a latent period of 2 hours, after which erythema appears. After heavy exposure, edema and even blisters may develop Histologically in the mildest reaction there is a bandlike zone in the uppermost layer of the epidermis with cellular damage nuclear pyknosis and vacuolation of the cells With more severe reactions, the zone of damage extends deeper leaving only the deepest 1-2 cell layers free In most severe reactions, the entire epidermis becomes necrotic, and bullous changes appear The cellular achromia may occasionally extend into the papillary bodies. The borderline of the tissue damage is always horizontal Changes in the cutis are limited to vasodilation, edema and moderate leukocytic emigration.

Reaction to long wave ultraviolet rays over 3,200 A is characterized by capillary damage and destruction of endothelial cells Leukocytes and round cells are absent or appear only in the periphery Collagen, elastic fibers and the entire epidermis remain undamaged. Visible and infra red rays in large doses cause necrosis by their caloric effect which goes deepest with red or short wave infra-red rays.

Phototoxic reactions due to photodynamic substances show two types Application and penetration of sensitizers from without cause a toxic lesion of the epithelium which differs from the classic ultraviolet light reaction by longer latency more pronounced gradation of effect and uneven damage. (2) If the sensitizers act from within the circulation ensuing changes are characterized by intensive reaction in the cutis, with edema, vasodilatation lymphocytic infiltration and connective tissue necrosis whereas the epidermis remains primarily intact and may be affected only secondarily

Photoallergic reactions are due to allergic manifestation

(4) Dermatologica 1 5 14 37 September 1937

sweating and follicular openings favor microbial growth at elevated environmental temperatures (forehead and temples, lower trunk forearms calves)

Remarkably low spreading values were obtained with lipid specimens collected from the clinically unaffected skin of 12 psoriatics. Similarly the acid number was low in many specimens from the psoriatics The cause of these findings is not known *Peculiarities in the microbial activity* on the clinically normal skin of psoriatics might be considered, but disturbed enzymatic activity inside the skin structures seem at least as probable.

Study of Fats in Normal and Pathologic Skin is presented by M Prunieras[5] Preliminary evaluation was made of various technics e g fixation of tissue several types of sudan stains particularly black sudan B and sudan IV and other reactions, such as Baker s test special mitochondrial tests *Schiff s reaction and the trypsin test Study of epidermal* fats led to the following conclusions (1) There are masked lipids in a perinuclear zone and in nuclei of malpighian cells (complex phospholipid nucleoproteins) (2) Phospholipids in intercellular spaces are distributed as nodules of intercellular bridges when these exist probably as a result of capillarity (3) Epidermal cells incapable of synthesizing them are surrounded by phospholipids probably of plasma origin (4) Penetration of lipids in the epidermis has been obser*ved in melanodendrocytes and their dendrites* (surface effect?) and in the course of exoserosis in eczema in vesicles being formed.

Exclusive of xanthomas and xanthomatous lesions and dyslipoidoses study of the dermal fats showed that (1) lesions of dermal allergies are usually accompanied by appearance of free fats in capillaries of the superficial layer (2) histiocytic cells react by phagocy*tosi of these free lipids so that* at a later phase *all free fat ha* disappeared *and intrahistiocytic fat has increased* (3) production of the e lipids might be due to a splitting of lipoprotein in edema fluid and (4) such splitting might be due to the action of proteolytic enzymes released by altered epidermal cells or to physicochemical imbalance in the extracellular portion of dermal connective tissue involving *the collagen mucopolysaccharide* complexes.

(5) Sem. des Hôp. Paris 33 26 39 Jan. 22 1 57

do not produce the complete histologic picture of basophilic degeneration. X rays may produce degeneration of the cutis but the effects are not exactly comparable with the elastosis of weather-beaten skin, and there is little ionizing radiation in sunlight that reaches the surface of the earth.

At first glance, the increasing incidence of basophilic degeneration with advancing age may seem to indicate a relation to senility per se. When considered with the other data collected in this study it indicates more properly that the relation is not to advancing years alone but to increasing time of exposure to the elements. Apparently the change does not occur abruptly. Use of the term "senile elastosis" or "senile degeneration" should be discontinued. The authors suggest such descriptive terms as "basophilic degeneration" or "elastosis," or if etiology is to be imputed, "solar" or "actinic elastosis."

► [A systematic study which supports the authors' suggestion that the terms "senile elastosis" and "senile degeneration" be discontinued and in their place "basophilic degeneration" or "basophilic elastosis" or even "solar or actinic elastosis" be used.—Eds.]

Experimental Eczema. Histologic Changes of Reactions Obtained by Transfer of Hypersensitivity were studied by A. de Weck and R. Brun[8] (Univ. of Geneva) in donor and receptor animals.

TECHNIC.—As donors, guinea pigs sensitized to dinitrochlorobenzene (DNCB) or to picryl chloride (PCl) were used. In the former group, the animals were sensitized by 11 daily applications of 1% DNCB in acetone, but only those animals were used which after such treatment showed a strong reaction to 0.1% acetone solution of DNCB. In the latter group, hypersensitivity to PCl was produced by a special method. The donor animals revealed positive reactions to 0.01-0.005% PCl in olive oil. Next, the transfer of cells of peritoneal exudate was obtained by injecting 20 cc. sterile paraffin into the peritoneal cavity of donors. After 48 hours, the animals were killed, and the exudate obtained by laparotomy was repeatedly washed with sterile Tyrode solution, centrifuged for 10 minutes, suspended in Tyrode solution and injected intraperitoneally into receptor animals. For transfer of blood cells, about 8 cc. blood was taken from donors by cardiac puncture and heparinized. The erythrocytes were separated by adding 3.5% polyvinylpyrrolidone in an amount 1½ times the blood volume by keeping the mixture for 1 hour at 37 C. The supernatant plasma, containing about 50-80% leukocytes, was pipetted and centrifuged. The sediment was resuspended in very little plasma and injected into the peritoneal cavity of receptor animals. The plasma was transferred by using the same method of separating and injecting the supernatant plasma into the peritoneal cavity of the

(8) Acta dermat.-venereol. 36:340-348, 1956.

elicited by antigens developing in the skin under the influence of light In photosensitive drug reactions (sulfanilamide, chlorpromazine) the drug probably constitutes the substance which by irradiation of the skin turns into an allergen. Sulfanilamide is changed into an allergen by oxidation of an amino radical in the benzol ring

The photoallergic reactions are of the urticarious or the eczematoid delayed type In a patient with cryptogenic eczema solare, Miescher elicited a reaction in a skin area not previously exposed to light with long wave ultraviolet light. Histologically this reaction showed the classic signs of an eczematoid reaction There was typical focal loosening of the epidermis starting from the basal layers and an impressive subepidermal accumulation of lymphocytes as seen only rarely to this extent in contact eczema

Basophilic Degeneration of Cutis Data Substantiating Its Relation to Prolonged Solar Exposure Herbert Z. Lund (Univ of North Carolina) and Robert L. Sommerville[7] (Mayo Found.) studied histologically pieces of skin from sites customarily exposed or customarily covered by clothing or hair from 2 white and 2 Negro cadavers In addition 502 skin biopsies were studied. The biopsies were classed as white or Negro and exposed or covered Basophilic degeneration was limited to the exposed parts of the body increased in degree with age and seemed to be less evident in the Negro The degree of change in exposed skin was greatest in sites that receive the most intense and prolonged solar irradiation and least in sites that are shaded

It is true that the drying effect of sun and wind may have similar correlations but it is doubtful that drying effect would account for some of the findings e g the abrupt changes in the degree of basophilic degeneration at the junction of the inner and outer surfaces of the ear On similar ground it is difficult to attribute the change to cold Further argument against cold is absence of basophilic degeneration in the skin of the feet and palms.

The element of sunlight responsible for the alteration is not known Since ultraviolet radiation is largely absorbed in the stratum corneum perhaps other wavelengths should be considered, as should the local heat produced by the sun. Although low-grade burns may alter the connective tissue they

(7) Am. J Clin. Path. 27 183-190 February 1957

the skin is made capable of responding to contact allergens with the intraepidermal changes which characterize true contact type allergic eczematous dermatitis in man in place of the nonvesicular noneczematous response of allergic guinea pig skin to contact allergens. This suggests that abnormal thickening of the prickle cell layer might also have an important bearing on allergic eczematous contact type dermatitis in man. Acanthosis could be one of the mechanisms by which nonspecific factors contribute to the genesis of eczematous dermatitis.

► [These studies, as well as those of Jadassohn, Brun and Bujard, Nilzén, Zelígman and others show that thick prickle cell layer increases the capacity of guinea pig skin to respond to changes which, while not grossly vesicular histologically in many ways resemble spongiosis and other features of eczema in man. This holds true whether the prickle cell layer is naturally thick (as in the guinea pig nipple) or is deliberately made acanthotic with agents such as Span 20 squalene and sodium lauryl sulfate.—Eds.]

Experimental Eczema Protective Effect of Acanthosis was investigated by A. de Weck and R. Brun[1] (Univ of Geneva) Acanthosis was produced in the nipples of male guinea pigs by applications of estrogenic hormones and on the flank by a mixture of cetyl and propyl alcohol in a non fatty base

Jadassohn showed that daily application of 1% chrysarobin for 30 days produced acanthosis and that in such acanthotic epidermis, the later application of 1% chrysarobin did not produce an inflammatory reaction. The authors confirmed this nonirritating effect of 1% chrysarobin on skin areas with acanthosis produced by the acanthogenic preparation, thus demonstrating that acanthosis protects against irritation due to chrysarobin.

Application of a 1% acetone solution of dinitrochlorobenzene (DNCB) usually productive of toxic primary lesions to the acanthotic flanks or nipples produced no significant reaction in most animals, although toxic reactions were occasionally produced, especially in animals showing an intense reaction on the opposite flank without acanthosis. When 2% acetone solution of DNCB was applied, the acanthotic flanks presented a primary toxic reaction which was less severe than on the nonacanthotic flank.

In animals previously sensitized to DNCB or picryl chloride (PCl) application of these substances to acanthotic

(1) Dermatologica [illegible] February 1957

animals. After splenectomy with the aid of a forceps, the spleen was torn into small pieces in a Petri dish containing Tyrode's solution the suspension of splenic cells was removed, washed in Tyrode's solution centrifuged and resuspended in Tyrode's solution and finally administered intraperitoneally. Receptor animals were tested 24-48 hours after injection by application to the flank and nipple of DNCB (0.1% in acetone) and PCl (1% and 0.1% in olive oil). The test areas were excised 24 hours later for histologic examination.

Contact hypersensitivity to DNCB could not be transmitted to guinea pigs by intraperitoneal injection of peritoneal exudate cells, blood cells, blood plasma or spleen cells originating from guinea pigs sensitized to DNCB. Guinea pigs intraperitoneally injected with spleen cells from donor animals sensitized in a special way to PCl showed strongly positive reactions. Histologically, the reactions observed on the flank or nipple of the receptor animals did not show true eczematous changes in contrast to marked contact dermatitis found in the donor animals.

► [Our own studies (see following abstract) revealed an absence of histologic features of eczema (e.g., spongiosis) in the unaltered skin of guinea pigs actively sensitized and exposed to dinitrochlorobenzene or picryl chloride. However, when the skin of these sensitized animals was deliberately made acanthotic, application of the allergen to such altered skin tended to cause eczema-like reactions with spongiosis.—Eds.]

Contact Dermatitis with Spongiosis and Intraepidermal Vesiculation in Acanthotic Skin of Guinea Pigs was produced by Rudolf L. Baer, Stanley A. Rosenthal and Charles Sims[9] (New York Univ. Post-Grad. Med. School and Skin and Cancer Unit). Based on the assumption that the skin of guinea pigs fails to respond with characteristic eczematous reactions to stimuli which produce them in man because of the thin prickle cell layer, the attempt was made to thicken this layer (produce acanthosis) by applying squalene, Span 20 or sodium lauryl sulfate in a 2.5% aqueous solution to 13 guinea pigs before using sensitizing substances. Test substances were picryl chloride (2% in olive oil) and 2,4-dinitrochlorobenzene (DNCB) (2% and 0.1% in acetone), which were applied to normal and acanthotic sites. Nine guinea pigs showed a reaction very reminiscent of eczema in man in the acanthotic sites after the test solution was applied, whereas there was a noneczematous reaction on normal sites or with the use of the vehicles only as control.

If acanthosis is deliberately produced in guinea pigs' skin

(9) J. Invest. Dermat. 27: 249-258, October 1956.

the skin is made capable of responding to contact allergens with the intraepidermal changes which characterize true contact type allergic eczematous dermatitis in man in place of the nonvesicular noneczematous response of allergic guinea pig skin to contact allergens. This suggests that abnormal thickening of the prickle cell layer might also have an important bearing on allergic eczematous contact-type dermatitis in man. Acanthosis could be one of the mechanisms by which nonspecific factors contribute to the genesis of eczematous dermatitis.

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(1) Dermatologica 1 91 101, February 1 57

nipples stimulated histologically typical eczematous reactions with spongiosis and vesiculation qualitatively identical with those in nonacanthotic nipples although they were perhaps a little less intense. Reactions produced with DNCB or PCl on the acanthotic flanks were more typically eczematous and easier to interpret than on the nonacanthotic flanks. "Cavitary changes" described by Leloir as typical of eczema in man were repeatedly observed. Also there were often small intraepidermal abscesses filled with polymorphonu clear cells which were not seen in such abundance in eczematous reactions on flanks of normal thickness.

Results of these experiments did not justify the conclusion that acanthosis plays a protective role as to the eczematous reaction in animals sensitized to DNCB or PCl. As to protection by thickened epidermis against irritation resulting from chrysarobin or DNCB it is impossible to say whether the essential role is due to acanthosis, to hyperkeratosis, or both.

► [In our studies (p. 456) acanthotic sites also showed a considerable degree of reactivity to tincture of cantharides, including microscopic blister formation. However, no systematic comparative tests were done with tincture of cantharides in acanthotic and nonacanthotic sites.—Eds.]

Acanthogenic Effect of Aliphatic Acids and Alcohols Applied to Flank of Guinea Pig. Because certain substances are known to produce acanthosis if applied to the flank of the guinea pig, R. Brun, Eug. Bujard and W. Jadassohn[2] (Univ of Geneva) studied the relation between the chemical formula and acanthogenic effect of certain normal aliphatic acids and alcohols in comparatively frequent use. Various aliphatic acids and alcohols with hydrocarbon chains of different lengths, both saturated and unsaturated (with one double bond), were applied to the skin in the experimental area 8 times in 10 days. At the end of this period, a biopsy specimen was taken for histologic study. Each substance was studied in 5 guinea pigs.

Measurement of the resulting acanthosis, if any, showed that the acanthogenic effect is, as might be expected, a function of the chemical formula. The significant elements are (1) the length of the hydrocarbon chain, (2) the presence or not of a double bond and (3) whether or not the substance is an acid or an alcohol. The acanthogenic effect of the unsaturated aliphatic compounds (double bond), both acid and

(2) Dermatologica 115:35-39, July 1957

alcohol, increases progressively with the length of the chain In the saturated series, on the other hand the alcohols produced little or no acanthosis, whereas with the acids the acanthogenic effect first becam clearly noticeable with C^8 It then rose to a maximum with C^{12} diminished sharply with C^1 and became nonexistent with the higher acids

Connection between Skin Irritating and Protein-Denaturing Effects of Some Surface Active Agents is discussed by Sven-Gosta Blohm[7] (Karolinska Inst., Stockholm) Emery and Edwards studied the influence of various sodium alkyl sulfates on the skin, using a homologous series of straight chain sulfates with from 8 to 18 carbon atoms. The skin irritating effect was discontinuous along the homologous series C^8 sulfate showed weak action C^{12} and C^{14} strong action and C^{16} and C^1 weak irritation. The results refute the widespread opinion that the shorter its carbon chain the more irritating a compound is

If protein denaturation plays a part in the process causing skin irritation it would be desirable to use the specific skin protein for n vitro analysis. Because such a protein has not been isolated, the author selected ovalbumin as a substitute The protein-denaturing effect of various alkyl sulfates was studied by measuring their capacity to uncover SH groups in ovalbumin. A protein-denaturation curve analogous in shape to the skin-damage curve of Emery and Edwards was obtained. Although it is too early to draw general conclusions from these findings it seems probable that protein denaturation plays a part in the skin irritating effect of the alkyl sulfates.

Blohm exposed a well-defined area on the skin for 1 minute to 1% sodium dodecyl sulfat (a sodium alkyl sulfate) and rinsed the area for 1 minute with water The area, including the surrounding skin, was then painted with a dye, 0.2% aqueous solution of indigo tetrasulfonate which combines with basic groups of protein. After rinsing with water the dye did not tak on the skin treated with the alkyl sulfate. This was interpreted as showing that the bas c groups in the epidermis had been blocked by sodium dodecyl sulfate.

► [It is amazing how few studies hav been done on the many effects of detergents on the skin Van Scott and Lyon (J Invest. Dermat. 21 199 1953) tested the sulfhydryl-exposing action of various soaps and nonsoap

(7) Acta dermat.-venereol. 37 264-273, 1957

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(2) Dermatologica 115:35-39 July 1957

ever it is conceivable that the reaction starts simultaneously in the epidermis and cutis but that the cutis shows the first changes because it is capable of developing its visible reaction faster In this connection it is stressed that both in the allergic and irritant responses the most conspicuous alterations in the rete were first seen in the midportion. If all epidermal reaction is secondary to the dermal changes, why do not the epidermal changes appear first in the basal cell layer adjacent to the cutis?

Observations in the eczema like reaction in guinea pigs lend some support to but cannot prove, the concept that the site of origin of the allergic contact reaction is in the upper cutis and that the characteristic eczematous changes of spongiosis and vesiculation are secondary to these events in the cutis. Such a course also would be in consonance with the hypothesis that the allergic contact type reaction and the 48-hour delayed tuberculin-type reaction, although not identical are expressions of a similar underlying immunologic process.

Histopathogenesis of Externally Produced Allergic Skin Reactions was studied by E. Bizzozero and M. Depaoli[3] (Univ of Turin) because the results of previous investigations were contradictory Some authors believed primary changes occurred in the epidermis, and others felt they occurred in the corium a third group reported no changes.

Skin specimens taken from persons strongly allergic to dinitrochlorobenzene (DNCB) were cut in halves, one-half being placed in Ringer solution and the other in Ringer solution containing 0 1% DNCB Results were completely negative. The skin pieces which had been exposed to DNCB solution for 4 8, 12 and 4 hours did not show any epidermal changes and no esiculette primordiale was seen

The findings of other observers included marked epidermal changes, g swelling of malpighian cells, pyknosis d sappearance of prickles i tercellular edema and vesiculation, as well as edema, dilated capillaries and perivascular infiltration in the papillary laye of the skin Therefore the authors assumed that the allergic reaction occurs essentially in the epidermis. The author n interpreting the findings of others, conclude that epidermal changes in allergic contact

(3) Hautarzt 7 447-450, November 1 56

detergents on keratin and concluded that these substances had a certain denaturing effect on the keratin molecule.—Eds.]

Allergic Eczema like Reaction and Primary Irritant Reaction Histologic Comparison of Their Evolution in Acanthotic Skin of Guinea Pigs Rudolf L. Baer Stanley A. Rosenthal and Charles F Sims[4] (New York Univ Post-Grad. Med School and Skin and Cancer Unit) produced acanthosis of the skin of guinea pigs by repeated application of squalene In the thus produced acanthotic skin of 26 guinea pigs observations were made of the evolution of the eczema like reaction to an allergenic agent (2 4-dinitrochlorobenzene) applied to one flank and the reaction to a primary irritant (cantharides tincture) simultaneously applied to the other flank. Biopsy specimens were taken simultaneously from both sides at 1 to 2 hour intervals during the early development of the reactions

The allergic eczema like reaction developed slowly and gradually the first changes becoming visible at about the 5-6th hour in the upper cutis. The subsequent changes were disturbances of the basal cell margin followed by intercellular edema spongiosis and vesiculation most pronounced in the midportion of the rete The reaction to the primary irritant under the conditions of this experiment was rapid and profound, severe damage being visible after 1 hour It was characterized by damage to the parenchyma including acantholysis Evidence of eczema like spongiosis was entirely lacking "Vésiculettes primordiales were not seen in either the allergic or primary irritant reactions

The authors point out that some of the observed differences could possibly be due to the different intensities of reaction rather than to differences in mechanism and that the results of histopathologic studies on the artificially acanthotic skin of guinea pigs are not necessarily applicable to the naturally occurring reaction in the skin of man

Judging conditions entirely on the basis of the present histologic findings it appears that the allergic eczema like response starts in the upper cutis and proceeds from there upward into the epidermis However it is possible that preceding the visible changes in the cutis (edema congestion) changes could occur first in the epidermis—changes neither histologically nor histochemically discernible More

(4) A.M.A. Arch. Derm 76 549-560, November 1957

over it is conceivable that the reaction starts simultaneously in the epidermis and cutis but that the cutis shows the first changes because it is capable of de eloping its visible reaction faster In this connection, it is stressed that both in the allergic and irritant responses the most consp c uous alterations in the rete were first seen in the midpor tion If all epidermal reaction is secondary to the dermal changes, why do not the epidermal changes appear first in the basal cell layer adjacent to the cutis?

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(5) [illegible] 7:487-499 November 1956

dermatitis are secondary those in the corium are primary

► [It is difficult to draw conclusions concerning the histologic site of the allergic reaction from such studies performed in vitro. However our own investigations (see preceding abstract) strongly support the views of Bizzozero and Depaoli that the primary phase of allergic eczematous contact sensitization probably starts in the upper cutis, even though the major histologic changes affect the epidermis.—Eds.]

Experimental Eczema Sensitization of Guinea Pig to Dinitrochlorobenzene (DNCB) and Picryl Chloride (PCl) was studied by A de Weck and R. Brun[6] (Univ of Geneva) using epicutaneous and intradermal tests With the epicutaneous test most chemical substances which sensitize the guinea pig also have a primary toxic effect Primary toxic reaction to DNCB or PCl on the flank of a nonsensitized guinea pig is difficult to distinguish macroscopically from an eczematous reaction on the flank of a sensitized guinea pig The only criterion for determining whether an epicutaneous reaction is due to sensitization is the concentration of the test solution. The primary toxic effect of DNCB does not depend solely on the concentration of solution applied, for tolerance varies in individual animals and in different strains The solvents used are also important Subtoxic concentrations of DNCB are 0 1% in acetone and alcohol and 0.5% in oil and of PCl in both oil and acetone 1% To avoid false interpretation of a reaction in a sensitized animal it is necessary to choose a concentration below the minimal primary toxic concentration The degree of sensitization can be evaluated from the intensity of reactions and from the minimal quantity of allergen required to stimulate a reaction Only significant differences should be considered

Histologic examination of the nipple is a reliable means of distinguishing sensitized from nonsensitized animals Reactions in nipples of animals sensitized to DNCB or to PCl are definitely eczematoid whereas reactions on the flank are often hard to interpret

The authors used two methods of sensitization (1) repeated applications of toxic concentrations and (2) injections of the allergen conjugated with protein plus adjuvants. Of 223 guinea pigs from different sources receiving 11 daily applications on the flank of a 1% acetone solution of DNCB 212 gave a positive reaction to 0 1% acetone solution 8 days after the last application The 11 animals with negative reactions gave a positive reaction after 5-6 supplementary ap-

(6) Dermatologica 113 335-368, December 1956.

plications of 1% solution. There was a striking difference in sensitizing capacity of DNCB and of PCl by skin application in acetone solutions. The PCl in acetone (1%) caused weak sensitization in only 1 of 6 animals. Sensitization was obtained, however, by 11 applications of 1% PCl in olive oil.

With the second method 64 guinea pigs were sensitized by nuchal injection of an emulsion of picryl guinea pig stromata (prepared by the method of Landsteiner and Chase), paraffin oil, BCG vaccine and anhydrous lanolin, followed by 3 applications of PCl (1%) in olive oil on the 21st, 28th and 35th days. Tests were performed the 42d day after injection. In 19 animals, 5 mg living BCG vaccine and 10 mg picryl stromata were used, and in 45 animals the amounts were increased to 15 mg dead BCG vaccine and 20 mg picryl stromata. Sensitization was obtained consistently with this method, but was less intense in the first series. Among 45 animals receiving the stronger emulsion, 13 reacted to a test solution of 0.01%.

The difference in eczematous reactions in guinea pigs sensitized by this special method and in those receiving skin applications is apparently in degree only. The reaction begins sooner if the animal is highly sensitized and if the test solution is more concentrated.

Other authors have shown that, depending on the sensitization method used, guinea pigs sensitized to DNCB or to PCl may show an anaphylactic sensitivity entirely different from the eczematous skin reaction. Picryl chloride is more active than DNCB with regard to protein in vitro and also with regard to anaphylactic sensitivity. In production of eczematous sensitivity DNCB in acetone, when applied to the skin, has a greater sensitizing power and primary toxic effect than PCl. A correlation exists between the sensitizing power of skin applications and the primary toxic effect.

[The editors regret an error which occurred in the abstract of the article by Frey and Wenk on pages 341-343 of the 1956-57 Year Book. In several instances the concentrations of test substances were given in per cent instead of per mil. It is suggested that the reader refer to the original article (Dermatologica 112: 265, 1956) for the correct figures.—Eds.]

Studies of Mechanism of Allergic Eczematous Contact Dermatitis. I. Findings on Human Skin with Radioactive Bichloride of Mercury are recorded by Victor H. Witten, Leonard D. Grayson and Vera H. Birnbaum (New York

(7) J. Invest. Dermat. 28:339-348, May, 1957.

Univ Post-Grad Med School and Skin and Cancer Unit) Autoradiograms of tissue sections prepared from biopsy specimens taken from areas of human skin tested with a solution of radioactive bichloride of mercury failed to show any differences in the sites of localization in the skin of persons known to be allergic to the compound and giving microscopically positive patch test responses as compared to those not allergic to the same compound and giving microscopically negative patch test responses. In both groups autoradiograms regularly demonstrated the radioactive mercury to be on the surface and within the epidermis, usually in the hair follicles and occasionally in sweat ducts There was no apparent concentration of radioactivity at any particular areas within the epidermal rete within the cutis nor in particular concentrations in relation to the sites of spongiosis the vesicles or blood vessels Although quantitative differences in the radioactive mercury deposits in the allergic as compared to the nonallergic persons are possible, the technic used would not permit such a fine differentiation

Using the columnated scintillation probe to measure radioactivity at about 48 hours after applying a radioactive bichloride of mercury patch test there was no demonstrable spread of the radioactive allergen from the patch test site in either allergic or nonallergic persons

Influence of Inhibition and Stimulation of Central Nervous System on Dinitrochlorobenzene (DNCB) Sensitization of Guinea Pigs was investigated by L. Polák[8] (Prague)

EXPERIMENTS.—*Influence of drug induced sleep*—To one group of guinea pigs, 0.2 Somnifene[*] was given intramuscularly and sen- [illegible] D[illegible] was done when the [illegible] wa [illegible] other [illegible] e the group, strongly sensitized gu[illegible] ea p[illegible] g[illegible] [illegible] experiment 1 flank of the animal wa depilated and divided into 2 halves. The temperature was taken in both areas every 15 minutes for 4 hours and again after a test dose was applied to the posterior half. The next day the other flank of the same animals was treated in the same way but before applying the test dose Somnifene wa administered.

In most of the animal te ted central inhibition by drug induced sleep prevented or strongly inhibited cutaneous DNCB sensitization The inflammatory reaction to the test

(8) Arch. klin. u. exper Dermat. 204 116 123, 1957

dose as far as differences in local temperature are concerned, was also inhibited by Somnifene® in guinea pigs sensitized while awake. These findings correspond to the influence of drug-induced sleep on various forms of inflammation (bacterial, chemical, actinic and allergic) and the effects of other sleeping drugs (Evipal®, urethan, etc.), hypnotic sleep and artificial hibernation on inflammation.

Experiments.—*Central nervous system stimulation.*—The methods used were: (1) *Continuous nociceptive* stimulation (0.03 ml. oil of turpentine injected every other day into the soles of the hind legs of guinea pigs). (2) Stimulation by electric current (50 volt impulses at interval of 30 seconds for 30 minutes twice daily, always preceded by bell ringing for 3 seconds) and (3) continuous physical exhaustion (induced in groups of 3 guinea pigs by forcing them to run in a rotating wheel continuously except for feeding interval of 1 hour each). Sensitization was started after 24 hours and test doses were applied daily 2 days after sensitization had occurred.

Results revealed that after methods 1 and 2 there were no differences in sensitization, whereas continuous exhaustion of the guinea pigs in the rotating wheel accelerated considerably sensitization to DNCB (stimulation of the cerebral cortex by continuous compulsory motion, lack of sleep, i.e., elimination of the physiologic protective inhibition). This finding is in full accord with the clinical observation that *nervous exhaustion or excitement influences* the course of dermatitis.

Cutaneous sensitization in newborn guinea pigs was no different from that of adult guinea pigs. It is, therefore, concluded that the central nervous system of guinea pigs is fully developed at birth.

► [The methods used in these studies to depress or stimulate the central nervous system of the test animals undoubtedly are capable of effects on other body tissues, including the blood vascular system, skin, adrenals, etc. Much more evidence would be required before one would be justified to conclude that the effect on one particular tissue, in this case on the central nervous system, is responsible for alterations in the normally expected immunologic events. Does forced running in a turning wheel affect only the nervous system? Or does it affect also the skeletal muscular apparatus, the adrenals and the lungs? All of the physiologic and biochemical changes which take place concomitantly as a result of administration of drugs or of subjecting the animals to physical exercise, must be considered as perhaps having an influence on the immunologic status of the animals. Schuppler and Storck (*Dermatologica* 112:419, 1956) observed that certain tranquilizing drugs affect allergic contact sensitivity in animals, but these authors were much more conservative in interpreting their results. —Eds.]

Univ Post-Grad. Med. School and Skin and Cancer Unit) Autoradiograms of tissue sections prepared from biopsy specimens taken from areas of human skin tested with a solution of radioactive bichloride of mercury failed to show any differences in the sites of localization in the skin of persons known to be allergic to the compound and giving microscopically positive patch test responses as compared to those not allergic to the same compound and giving microscopically negative patch test responses In both groups autoradiograms regularly demonstrated the radioactive mercury to be on the surface and within the epidermis, usually in the hair follicles and occasionally in sweat ducts There was no apparent concentration of radioactivity at any particular areas within the epidermal rete within the cutis nor in particular concentrations in relation to the sites of spongiosis the vesicles or blood vessels Although quantitative differences in the radioactive mercury deposits in the allergic as compared to the nonallergic persons are possible, the technic used would not permit such a fine differentiation

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EXPERIMENTS.—*Influence of drug-induced sleep*—To one group of guinea pigs, 0.2 Somnifene[®] was given intramuscularly and sensitization with a 5% solution of DNCB in acetone was done when the animals were fast asleep a test dose of 0.25% DNCB in acetone was applied when the animals were awake at feeding time. In another group, strongly sensitized guinea pigs were used 24 hours before the experiment 1 flank of the animals was depilated and divided into 2 halves. The temperature was taken in both areas every 15 minutes for 4 hours and again after a test dose was applied to the posterior half. The next day the other flank of the same animals was treated in the same way but before applying the test dose Somnifene[®] was administered.

In most of the animals tested central inhibition by drug induced sleep prevented or strongly inhibited cutaneous DNCB sensitization. The inflammatory reaction to the test

(8) Arch. klin. u. exper Dermat. 204 116-123, 1957

energy/Gm. this is nearly equivalent to 1 rep or 1 r) The polonium isotope $_{84}Po^{210}$ has a half life of 138 days. The isotope emits alpha particles of 5.3 Mev energy To avoid contamination of the skin by the polonium plaque it was covered with a sheet of 25-gauge Mylar film.

Irradiation of normal human skin from its surface with Po^{210} produced a clinical biologic effect of erythema and pigmentation. The erythema faded on diascopy indicating that it probably results from dilatation of superficial blood vessels of the dermis. It appeared within 2-8 hours reached a maximum between 8 and 20 hours then faded No second wave of erythema was observed.

It may be speculated that there is a theoretical threshold erythema dose for alpha radiation at about 20 000 rad. The barely perceptible erythema dose for polonium alpha radiation is about 75,000 rad. The larger the dose, the shorter the latent period for appearance of erythema. Considerable individual variation in erythema response to polonium was observed.

Depth dose measurements in Mylar indicate that at a thickness of about 4 mg./sq. cm. the dose is only 0 001% of the surface dose On the assumption that 1 mg./sq cm. Mylar is equivalent to a thickness of 10 μ of tissue, then at a depth of 40 μ only 0.001% of the surface dose would remain. If this assumption is correct, then measurements of the thickness of the epidermis indicate that almost all alpha radiation from polonium would be absorbed in the epidermis. It is possible that some penetration may occur in a few areas where thickness of the epidermis is less than 40 μ.

Many of the gross characteristics noted for erythema produced by Po^{210} closely resemble those of ultraviolet radiation but bear little resemblance to erythema caused by beta, gamma and x radiation. The mechanism by which the alpha particles produce erythema is unknown. If the visible biologic effects of erythema and pigmentation are the result of irradiation primarily of the epidermis, then the thinking regarding the biophysics of superficial irradiation of the skin warrants reconsideration For example, to account for the visible erythema, it might be necessary to consider the epidermal production and liberation of a diffusable substance, which in turn acts to dilate the dermal blood vessels.

Although alpha radiation in the form of thorium X has

Influence of Total Body X irradiation on Epidermal Hypersensitivity Correlation with Lymphocyte Response. Kenneth H Burdick* (7100th USAF Hosp Wiesbaden, Germany) was unable to detect significant changes in guinea pig sensitivity to 2 4-dinitrochlorobenzene (DNCB) when the chemical was applied after 100 r total body irradiation, regardless of the time between application of the chemical and irradiation There was slight increase in the time necessary for the erythema of the allergic reaction to develop in animals tested within 24 hours after irradiation

At a level of 200 r of total body irradiation the general degree of reaction to DNCB was similar to the preradiation control level except in animals exposed to the chemical within 48 hours of irradiation when again delay in allergic response was noted At the 300 r level ability of the skin to react to DNCB was reduced or abolished for the first 3 days. Reactions after 7 days were uniformly positive and in some instances at 10 days were more severe than the animal's own preirradiation control reaction This occurred despite clinical evidence in the animals of irradiation sickness depressed granulocyte counts and hemoglobin levels. Use of croton oil solutions diluted to the point where only mild erythema was noted in normal animals brought about no change in the time of appearance of erythema due to chemical irritation

Repeated blood counts for several days after irradiation in the experimental animals revealed that loss of lymphocytes after x ray treatment and subsequent recovery closely paralleled the ability of the skin to react to DNCB

► [*From the experimental point of view it is interesting that total body irradiation can alter the local allergic response of the skin to DNCB in previously sensitized animals but that irradiation of a localized skin site with the same x-ray dose has no effect on the allergic skin response. Any benefits that may be noted to follow treatment of allergic contact dermatitis with small fractional doses of x-rays obviously are not the result of alteration in the local allergic mechanism but are due to action on whatever tissue changes may have taken place.*—Eds.]

Erythema Effects of Polonium Plaque (Alpha Emitter) on Human Skin were studied by Victor H Witten William S Wood and Robert Loevinger[1] (New York Univ Post Grad. Med. School and Skin and Cancer Unit) The average surface dose rate of the *polonium plaque* was *300,000 rad/minute*, on the reference date (1 rad equals 100 ergs absorbed

(9) Acta dermat.-venereol. 37 110-117 1957
(1) J. Invest. Dermat. 28 199-210, March, 1957

events such as time of onset and duration of erythema, can be used as criteria of biologic effects in human skin, then the similarities in time of appearance and course of erythema after ultraviolet radiation and of erythema after polonium alpha radiation can be interpreted as indicating that these two forms of radiation produce similar biologic effects in human skin

Histology of Mouse Skin after Single and Fractional High Doses of X-rays was studied by F Kroning[1] (Gottingen Germany)

Method.—The dorsal skin folds of black mice were irradiated while the other parts of the body were screened. Single and fractional doses of 48,000 (8×6 000) were given, also 96,000 either as single or fractional doses (16×6,000) Within 25 (twice weekly) and 50 day (once weekly), 8×6,000 r and within 76 and 90 days, 16×6 000 ere given, using 50 and 180 kv Intensity was 4,000 r/minute with 50 kv and 1,000 /minute with 180 kv The mice were not killed, but specimens from li ing animals were examined histologically After fixation in formol (1:9) methyl benzoate-celloidin-paraffin sections (usually every 10th section) 10 μ thick were studied. If nodular arty lesions or ulceration existed, every 3d section wa studied or even serial sections were studied.

\ hi tologic differences were found regardless of whether 50 o 180 k irradiation was used, nor were any differences seen when 8 fractional doses of 6,000 r were given within 25 or 50 days or 16 doses of 6 000 r within 76 or 90 days. After pplication of 48,000 and 96,000 r to the dorsal skin fold, the macroscopically and histologically recognizable damage to the skin was more marked after a fractional than after a mgle pplication of h gh dosage Destructi e changes wer also longer lasting after fractional doses.

These esults are not in agreement with the general opin ion f radiologists that fractional application of a gi en x ray dose has milder less damaging effects on tissues including the skin Thi may be explained by the fact that the skin of laboratory animals is more radioresistant than human skin In rradiation of skin folds of black mice with high doses f x-ray fractional doses ha e no additi e effects but they exceed effects of the pplied ingle high dose. When 16 doses of 6,000 r were gi en skin damage was so severe after the 8th dose that an nterv l was required before x ray could be continued. After fractional irradiation of kin folds, the tumor incidence was h gher than after a ingle high dose After

(Hautarzt 7 504 510 November 1956

been in clinical use for over 40 years there is no known case of serious late sequelae such as ulceration and malignancy Such sequelae are not uncommon with large doses of conventional gamma and x radiation This pronounced difference in effect suggests that the biophysics of alpha radiation may be fundamentally different from that of conventional x radiation For these and other reasons, the biologic effect of alpha radiation applied to the skin surface must receive further study

► [The concept of a diffusable substance playing a role in the production of radiation erythema is not new That it definitely is a part of the mechanism by which ionizing radiation produces erythema has, to our knowledge, not yet been proved.—Eds.]

On Mode of Action of Alpha Radiation from Polonium[21] on Human Skin. Victor H Witten, Marion B Sulzberger and William S Wood[2] (New York Univ Post-Grad Med. School and Skin and Cancer Unit) studied the effect of different doses of alpha radiation delivered to different skin depths by adjusting the time of exposure to a Po^{210} plaque and by interposing Mylar film in various thicknesses between the plaque and the skin surface to reduce the depth of penetration of the alpha particles It was shown that ionizing radiation from the alpha particles of Po^{210} is capable of producing biologic effects of erythema and pigmentation when applied to the surface of human skin The biologic effects can occur when the alpha particles are prevented from reaching the cutis and irradiate only the epidermis Time of onset of erythema varied from 2 to 4 hours and was not affected by depth of penetration Erythema reached a maximum between 8 and 24 hours after which it began to fade By 72 96 hours erythema was completely obscured by pigmentation that lasted many weeks Duration of erythema and onset of pigmentation were not affected by dose

The nature of the change occurring within the epidermis are unknown Among the changes that must be considered are production of secondary radiation and possible formation of new chemical substances within the epidermis which in turn act on the superficial blood vessels of the cutis to produce erythema Clinical change in the skin after exposure to ultraviolet light are similar to those noted after application of Po^{210} except that the pigmentation produced by ultraviolet fades more rapidly If the clinically discernible

(2) Dermatologica 115:461-470 October 1957

events, such as time of onset and duration of erythema can be used as criteria of biologic effects in human skin then the similarities in time of appearance and course of erythema after ultraviolet radiation and of erythema after polonium alpha radiation can be interpreted as indicating that these two forms of radiation produce similar biologic effects in human skin

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No histologic differences were found regardless of whether 50 or 180 kv irradiation was used, no were any differences seen when 8 fractional doses of 6,000 were given within 25 or 50 days or 16 doses of 6,000 r within 76 or 90 days. After application of 48,000 and 96 000 r to the dorsal skin fold, the macroscopically and histologically recognizable damage to the skin was more marked fter a fractional than after a single application of high dosage. Destructi e changes were also longer last ng after fractional doses.

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(3) Strahlentherapie 7 94 3 8, November 1954

irradiation of the entire body surface with 4000 r in fractional doses the tumor rate was higher (19%) after 80×50 r than after 8×500 r. No epilation was seen after 8×500 r nor after 80×50 r. After 8×500 r fractional irradiation of the entire body surface the hair of black mice was markedly intermingled with white hairs and appeared silvery whereas after 80×50 r it appeared only grayish. Histologically the skin and its adnexa in these animals showed no changes except some anomalies of pigmentation.

► [These findings must be evaluated carefully keeping in mind the author's statement that the skin of laboratory animals is more radioresistant than human skin. Furthermore, one cannot help but suspect that the reaction of mouse skin to x radiation may differ in other ways as well from that of human skin. These results, then, cannot be accepted as necessarily applying to the skin of man.—Eds.]

First Observations on Increased Biologic Activity of X-rays as Function of Changes Induced in Surface Tensions of Living Tissue. Guido Farris and Luigi Oliva[4] (Univ of Genoa) discuss the results of experiments which seemed to indicate that a substance with a general radioprotective activity has locally the opposite action. When they tested the radioprotective action of an ointment containing 10% beta mercaptoethylamine (MEA) incorporated in petrolatum glycerin Tween® 40 ethyl alcohol and water the erythema and ulceronecrotic lesions caused by the x rays were more severe on the skin areas to which the ointment had been applied. This suggested that the changes in surface and interfacial tension induced in the cutaneous tissues by the Tweens® were responsible for the increased action of the x rays. Experiments on guinea pigs showed that irradiation induced erythema appears earlier and is more intensive and widespread on the skin area to which Tween® 40 and Tween® 80 was applied either before or immediately after the irradiation.

In discussing the tissue alterations caused by the action of the tension-changing substances the authors assume that the presence of such substances in the tissues may modify the physicochemical equilibrium of the complex cell structures and permit or facilitate the passage through the interfacial barriers of substances that generally cannot traverse these barriers because of their heterogeneous constitution. It may also be that the action of the tension-changing substances increase the rate of diffusion within the tissue. They

(4) Radiol. clin. 26:221-228, July 1957

explain their results as follows The free active radicals, produced in the tissues by irradiation through ionization of water are capable of modifying some biochemical structures that are especially receptive. These structures are responsible for the tissue lesions secondary to irradiation. The easier the contact between the damaging substances produced by irradiation and the most delicate constituents of the living cell, the greater the damaging action of the irradiation. The specific action of tension-changing substances on some dyssymmetrical interfacial structures will combine with a homologous, if not identical, action of the irradiation and thus cause more pronounced alterations of the equilibriums of permeability of the tissue biochemical structures than irradiation alone.

► [Since Tweens® are used in some of the modern topical medicaments, these findings may have practical implications therefore, studies on the skin of man are desirable.—Eds.]

Method of Measuring Erythema and Pigmentation of Skin. Evaluation of various degrees of cutaneous erythema and pigmentation was unsatisfactory until direct photometry of light reflected from the skin was used. In direct photometry the test area of the skin and a magnesium oxide surface ("white standard") are exposed to the same light source at the same distance and light reflected from both skin and white standard are compared and measured. H J Heite and G. Weber[3] (Univ of Marburg) report experiences with "Elrepho (Carl Zeiss) an electric, high precision photometer for measuring reflected light.

APPARATUS.— Elrepho is based on the principle of the photometric sphere of Ulbricht, a hollow sphere of about 15 cm. diameter with white inner wall and 2 lateral light bulbs. There are 2 windows in the wall, to 1, the gauged white standard and the skin to be tested are pressed while the other constantly exposes the white inner wall of the sphere. Light rays reflected from these 2 areas are received by 2 photoelectric cells connected with each other so that, in case of exposure to different light, differential currents appear which, when amplified, are shown on a scale. The photoelectric cells may be used for measuring within a spectral range up to 700 mμ, but can be exchanged for others sensitive in the ultrared spectral range up to 1μ. Besides, the set is equipped with 7 light filters (420, 460, 490 530, 570, 620 and 700 mμ) of which those with permeability for 490 or 530 mμ wavelengths were chiefly used.

For measuring remission values of the skin (diminution of light reflection by the skin) not the white standard, but a

(3) Arch. klin. u. exper Dermat. 204:117 139 1957.

secondary (auxiliary) standard was used *consisting of an approximately skin-colored, yellow red cardboard (with* λ *representing a remission value of 55-60% at 530 mμ)*

Measuring was done mostly on the volar aspect of the forearm 10 single remission values (ξ) of each area were ascertained and the average value ($^{\xi}$) corrected with the remission factor of the auxiliary standard

$$x = \frac{\lambda \bar{\xi}}{100}$$

In three instances the usefulness of the described method and the advantage of clinical routine measuring of erythema is shown (*1*) A patient with acrodermatitis chronica atrophicans was treated with penicillin remission values after 12 days revealed a distinct decrease of the erythema i.e., abnormally low remission values caused by the erythema were seen to rise again (*2*) The varied course of ultraviolet erythema in a normosensitive test person and in a patient with sun dermatitis was demonstrated In the former the beginning erythema could be measured 2 hours after irradiation when it was clinically not noticeable reached its peak *after 6-8-10* hours and returned to initial values within 36 hours. In the latter the erythema was unchanged after 96 hours and the remission values were still low (3) Cutaneous changes produced by topical application of rubriment a nicotinic acid ester occur rapidly and vary considerably as to color (paleness or erythema) or edematous elevation (wheal formation) Besides various persons and skin areas may respond differently to nicotinic acid esters Classification of the course of such fast and widely different reactions is difficult because of subjective misreading or misremembering but are considerably facilitated by objective measuring of erythemas (or pigmentations)

► [There is indeed a great need for device which can accurately measure erythema and pigmentary changes in human skin Such an instrument must be simple to operate the readings must be reproducible and it must be capable of differentiating the erythema and pigmentation produced by the disease or reaction under investigation from that normally present at the site. The normal variations due to existing pigments, vascularity degree of oxygenation of blood, etc. must be considered These factors can cause the skin color in any one patient to vary from site to site and from time to time Therefore, it is not enough to use secondary standard in addition a nearby control site should also be measured for comparison. —Eds.]

Factors Affecting Diffusion of Drugs from Vehicles to Skin Surface were investigated by J B Shelmire Jr (Southwestern Med. School) Tracer substances that stain the skin were incorporated into 6 different vehicles. Relative intensity of skin color after a fixed period (2 hours) determined the rate at which the tracer diffused from the vehicle to the skin surface. Vehicles used were (1) Carbowax 1500 a nonvolatile water miscible base (2) high viscosity carboxymethyl cellulose an aqueous base (3) Velrachol, an oil-in-water emulsion (4) Polysorb Hydrate, a water-in-oil emulsion (5) hydrous lanolin a water in-oil emulsion and (6) Aquaphor* an anhydrous absorption type base that will form a water-in-oil emulsion The tracers were (1) acid fuchsin, a water-soluble dye (2) sudan III an oil-soluble dye and (3) vitamin A, which is water insoluble but oil soluble In addition, the irritative effect of 5% salicylic acid was observed when incorporated in each vehicle.

The study showed that two important factors determine the diffusion rate of a substance from vehicle to skin surface degree of hydration of the skin or vapor pressure at the skin vehicle interface and miscibility of the vehicle with skin secretions. Solubility in the vehicle and compatibility with the vehicle are other important factors. Hydration of the skin surface may depend on formulation type of covering atmospheric conditions and thermogenic sweating which varies with the site of application. Miscibility of the vehicle with sweat is important not only because of its effect on skin hydration but also because it determines the rate of release of a drug from the water in-oil emulsions Miscibility with superficial skin lipid appeared to be of little importance because their removal did not alter results obtained. This probably is because the skin lipids are for the most part dispersed in sweat at the skin vehicle interface and do not exist as a continuous film

Water-soluble dye showed greatest diffusion to the skin surface from those vehicles that were easily miscible with sweat and maintained an aqueous skin vehicle interface. An oil-soluble dye and vitamin A diffused best from a nonvolatile water miscible vehicle which maintained least hydration of the skin-vehicle interface Salicylic acid caused

(C) J. Invest. Dermat. 27 313 317 December 1956.

the most pronounced irritative reaction in a water-in-oil emulsion.

► [An interesting series of in vivo studies, accomplished without elaborate equipment. Previous experience has shown, however, that the clinical efficacy of medicaments does not necessarily parallel the ease of release from various vehicles or the penetration as shown experimentally.—Eds.]

Behavior of Radioactive Sulfur after Its External Application to Skin is reported by A. Scott[7] (St. Bartholomew's Hosp., London). The radioisotope S^{35} was used to show absorption and localization of sulfur in the normal skin, to determine alteration in behavior of the isotope in presence of a dermatosis such as seborrheic dermatitis, acne vulgaris and psoriasis, and to observe the effect of routine therapy of the lesions on previously observed behavior of sulfur.

Of 70 patients tested, 12 were normal controls, 18 showed seborrheic dermatitis, 18 acne vulgaris, 8 psoriasis and the others eczema, lichenification, ultraviolet irradiation and discoid lupus erythematosus. Contact Geiger countings were taken before covering the area and after removing the patch at the end of the experiment to yield a quantitative measure of the sulfur retained in the skin. Autoradiographs were made of biopsy specimens to present a visual record of the position and disposal of the sulfur. The ointment used incorporated radioactive S^{35} with a half life of 88 days in a hydrous emulsifying ointment (British Pharmacopoeia) together with 2% of stable sulfur as a carrier. 100 mg. of the preparation contained 5 μc. radioactivity.

Normal skin was readily penetrated by S^{35} with no preferential absorption by the appendages. Within 24 hours of application the sulfur had disappeared from the dermis, suggesting *systemic absorption* probably *through intercellular* substance rather than by intracellular absorption. In seborrheic dermatitis S^{35} appeared to be concentrated just deep to the midepidermis but none entered the basal layer. It was disposed of by outward transfer and showed an *intracellular* concentration.

In acne vulgaris, although the sulfur penetrated the epidermis as in the normal cases, it showed concentration in the hair follicles and accumulated in the undischarged contents of the sebaceous glands. Once the sulfur reached the glands, it stayed there for as long as 3 weeks and there

(7) Brit. J. Dermat. 69:39-49, February, 1957.

seemed to be no reabsorption of sulfur from the glands. Geiger counts over the glands gave about 10 times the value obtained in normal skin. In a psoriatic lesion sulfur penetrated the epidermis as far as the basal layer and gave counts of radioactivity 20-40 times that of the normal. Little entered the dermis, the greater amount being disposed of by passing out through the epidermis. The absorbed sulfur was intra cellular The miscellaneous lesions mentioned showed little difference from the normal skin.

The tests were repeated during the course of improvement n the lesions with therapy In seborrheic dermatitis, the depth of penetration of sulfur gradually increased until the basal layer was reached, and the tendency for material to accumulate in the midepidermis disappeared. When the disease was clinically healed, movement of the sulfur corresponded to that in normal skin and tendency to intracellular localization ceased. In acne vulgaris there was no change for as long as the sebaceous glands persisted, the sulfur accumulated in their contents. In cleared psoriasis, the sulfur pattern also returned to normal.

The question s raised about localization of sulfur in the midepidermis, and about its action in an intracellular sulfhydryl-containing enzyme system

[One wonders what the effect of testing in different skin sites would be. For example, sites of acne would be expected to have more sebaceous glands and, therefore, might behave differently Also, is it possible to distinguish in autoradiograms between the inter and intracellular localization of radioactive sulfur?—Eds.]

Percutaneous Absorption of Cortisone-4-C through Normal Human Skin was established by F ederick D Malkinson, Edward H Ferguson and Ming C Wang[3] (Univ of Chicago) who detected radioactivity in the urine after application of cortisone-4-C^{1} acetate incorporated into an ointment base. Peak excretion of radioactive material occurred in the first 24 hours after pplication but lower levels of radioactivity persisted throughout an experimental period (6-7 days. Comparison with previous studies of the percutaneous absorption of hydrocortisone-4-C^{14} indicates that penetration of cort sone and hydrocortisone into the skin are closely similar qualitatively and quantitatively

Distinct elevation in excretion of both hormones shortly after application and rise n cort sone-4-C^{14} excretion after

(3) J. Invest. Dermat. 28 211 216, March, 1957

vigorous removal of the ointment probably reflect transfollicular absorption from mechanical introduction of radioactive hormone into the hair follicles The persistent but lower levels of urine activity throughout the period of ointment contact with the skin indicate continuous transepidermal or transfollicular absorption of hormone Both the hydrocortisone-4-C^{14} and cortisone-4-C^{14} studies showed that less than 1% of the applied hormones could be demonstrated in the urine.

As cortisone and hydrocortisone are similarly absorbed through the skin it is apparent that the contrasting therapeutic effectiveness of these hormones is due to differences in their metabolism *in the skin It is probable* that one or more antiinflammatory metabolites specific for hydrocortisone are formed in the skin.

► [A long awaited study, which in combination with the previous investigations of Malkinson and Ferguson on the percutaneous absorption of hydrocortisone-4-C^{14} ointment, is strong evidence that the therapeutic effectiveness of topical hydrocortisone preparations is not dependent on its rate of absorption. The fact that less than 1% of these hormone products is shown in the urine leaves 99+% to be accounted for.—Eds.]

Quantitative Studies on Cutaneous Absorption in Warm Blooded Animals with Radioactive Isotopes—*II Influence of skin condition on absorption*.—H Kutzim[9] (Univ of Cologne) studied skin absorption in rats Normal skin covered skin skin defatted by ether or skin showing dermatitis produced by cantharidin was used and the method described in an earlier study was followed

Absorption of NaI^{131} from an ointment base was small (about 10.7%) in normal skin after 24 hours the skin remaining histologically normal Absorption was 2.7 times increased after 8 hours when the skin was covered. Increased absorption by covered skin is associated with swelling i e marked epidermal enlargement after 6-10 hours, involving particularly the horny but also the basal prickle and granulosum layer An additional increase of cutaneous absorption was found when the skin was not only covered but also defatted by ether After 10 hours in the defatted and acanthotic skin only 15.2% of NaI^{131} remained. An unexpectedly high absorption occurred in a skin with dermatitis produced by applying a cantharidin plaster 24 hours before testing After 15 minutes, only 61.5% of NaI^{131} was found.

(9) Arch klin u exper Dermat. 203 323 329 1956.

III Influence of ointment bases on absorption —Kutzim investigated the influence of various ointment bases on absorption by the normal skin of rats, skin showing swelling (acanthotic changes) and skin showing changes of oozing dermatitis. The method was that used in previous studies.

Investigation as to the absorption of NaI^{131} revealed several important facts. (1) Ointment bases arranged in order of decreasing influence on cutaneous absorption by normal skin were petrolatum, silicon oil-in-water emulsion and polyethyleneoxide (cremolan) For skin with inflammatory changes (oozing dermatitis) the serial order was reversed. Thus in normal and acanthotic skin, the absorption from lipophilic ointment bases proved to be superior and in skin with inflammatory changes, the absorption from hydrophilic ointment bases was better (2) The influence of ointment bases on absorption of incorporated NaI^{131} is rather insignificant and less important than the condition of the skin. (3) The same results as with NaI^{131} were found when Na_2HPO_4 (P^{32}) and water-soluble penicillin were incorporated

In normal skin, ointment bases because of their covering effect, create acanthotic changes and thus better absorption of the incorporated substances. The degree of absorption parallels the degree of acanthosis.

Experimental Production of External Otitis in Man by maceration, primary irritants and allergic contactants is reported by Walter B Shelley and Eldon T Perry[§] (Univ of Pennsylvania) Among 79 normal adult men, ear plugs were placed in 1 external auditory canal of each of 8 adhesive tape was placed on the wall of 1 canal of each of 14 and tape and rubber ear plugs sealed the canals of 24 Formalin, first 2% and later 4% was swabbed on the ear canals of 12 Halowax 1014 in a 50% concentration in mineral oil was applied to the canals of 11 and a 1 100 aceton dilution of 3-n-pentadecylcatechol was used as an open patch test on the canals of 10 to produce minimal allergic reaction. Biopsy specimen were taken from all areas

Maceration dermatitis was produced by the tape and plug reproducing the otitis seen in the tropics where heat and humidity are causative factors. Removal of plugs produced

‖ Arch Klin u exper Dermat 204 12 36, 1957
§ J Invest Dermat 27 261 269 November 1956.

prompt healing a rapid reversal of the soggy tropical ears. No findings of miliarial syndromes were related to the plugging of the apocrine glands of the external ear No true pyodermas or fungous infections were seen. Both Formalin and Halowax produced eczematous reactions the latter showing remarkable comedone formation The experimental production of low-grade contact dermatitis on an allergic basis using penta-decyl-catechol was manifest by pruritus and erythema but was otherwise clinically inapparent. Yet histologic studies showed spongiosis and microvesiculation of the follicular walls with a normal epidermis. Thus biopsy of the canal can be significant in diagnosis of dermatitis venenata.

► [The production of "tropical or "hot weather ear by simple occlusion, without associated pyodermas or fungous infections, and the prompt healing that follows removal of the plugs is of considerable clinical importance.

In a dermatologic practice it is not at all unusual to see external otitis which may be iatrogenic in origin. This may be from incorrect treatment or overtreatment of otitis believed to be of infectious origin. In reality the eruption may have been due to plugging with subsequent inflammatory reaction or to a dermatologic disorder such as psoriasis, seborrheic dermatitis etc. It is necessary to consider all possible causes of external otitis before starting therapy —Eds.]

Evaluation of Factors Which may be of Importance in Production of External Ear Infections. Ben H Senturia and F M Liebmann[3] (Washington Univ) studied the effect of infection with Pseudomonas aeruginosa high temperature high humidity removal of lipids and trauma in production of experimental ear infections in cats The various factors were used singly and in various combinations It was possible to produce fairly consistently infection of the external ear canal with morphologic findings and pathologic changes similar to those found in human beings As in man variation in susceptibility to infection was noted. No single factor consistently produced inflammatory changes in the skin of the external ear but infection with pseudomonas organisms was found to be a necessary factor when combined with trauma and/or lipid removal

High temperature and elevated humidity did not increase the degree of inflammatory changes produced by other factors. This is contrary to firmly established empirical observations in man and apparently indicate that the skin lining the ear canal of the cat reacts differently to elevated temper

(3) J Invest. Dermat. 27:291 317 November 1956.

ature and high humidity than does the skin of the human ear canal.

Bacteriologic studies did not confirm the observations that gram-negative bacilli disappear rapidly from the surface of healthy untreated skin. Once contamination occurred, positive cultures persisted for long periods and the rate of disappearance could not be correlated with any factor tested. This would agree with the great difficulty in eliminating this organism from the human ear canal after acute external otitis although the ear canal clinically appears free from disease.

► [The human ear canal is also subject to various dermatoses, such as psoriasis, seborrheic dermatitis, allergic contact dermatitis and atopic dermatitis. These dermatoses may create a suitable terrain, which together with various other factors, including those discussed by Senturia, may result in otitis externa.—Eds.]

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